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June 1, 2014

Chairman Fred Upton
Chair, Energy and Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Representative Dianna DeGette
2368 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Upton and Representative DeGette,

On behalf of the nearly 35,000 members of the American Society of Clinical Oncology (ASCO) who specialize in the treatment of patients with cancer, I commend you for launching the 21st Century Cures Initiative to examine how to accelerate the discovery, development, and delivery of promising new treatments to patients. I am pleased to provide input on the first white paper, 21st Century Cures: A Call to Action.

As ASCO celebrates its 50th anniversary this year, we reflect on the tremendous progress made in cancer treatments over that time. The number of drugs available to treat cancer has grown from a small handful to more than 170, many of which are far more effective and less toxic than previously available treatments. Today more than two-thirds of patients with cancer are alive five years after their diagnosis, compared with less than one-half in the 1960s. There are now more than 13 million cancer survivors alive in the United States (US) and this number is growing.

Despite these achievements, there remain many unmet medical needs for cancer patients, and this is not the time to slow development. This year, an estimated 1.6 million Americans will be diagnosed with cancer. In 2013, about 580,000 American lives were lost to cancer. The population is growing, aging, and more overweight, making it likely that cancer will take over heart disease as the leading cause of death by 2030.

ASCO appreciates the work of the Office of Hematology and Oncology Products (OHOP) led by Dr. Richard Pazdur at the Food and Drug Administration (FDA). OHOP oversees development, approval, and regulation of drug treatments for cancer, therapeutic biologic treatments for cancer, therapies for prevention of cancer, and products for treatment of nonmalignant hematologic conditions.

Scientists within OHOP are working on incorporating innovations in pharmacogenomics, bioinformatics, and clinical trial design into the drug review process. ASCO has cosponsored workshops with OHOP and others to better measure

the status of disease in patients with leukemia, define surrogate endpoints for neoadjuvant breast cancer trials, educate scientists and advocates about anticancer agent development, and convene stakeholders to create a genomic-based master protocol for metastatic breast cancer trials. OHOP has been a leader within FDA in using approval pathways such as Accelerated Approval to get drugs to patients faster, and has quickly adopted new programs such as the Breakthrough Therapies Designation. These efforts have contributed substantially to accelerating the introduction of new treatments for cancer into practice. ASCO is concerned, however, about the ability of the FDA in general and the OHOP specifically to continue to expand the scope and quality of their work without additional resources.

ASCO's 2011 report, *Accelerating Progress Against Cancer: ASCO's Blueprint for Transforming Clinical and Translational Cancer Research*, presented a vision for cancer research and patient care to become more targeted, efficient and effective. The Blueprint, attached, contains recommendations that address many of the issues the 21st Century Cures Initiative is exploring:

1. Establish a new approach to therapeutic development, driven by our more thorough understanding of cancer biology and the advent of new technologies.
2. Design smarter, faster clinical trials to provide evidence for effective treatments targeted to patients most likely to benefit.
3. Harness advances in health information technology to seamlessly integrate clinical research and patient care.

Subsequently, ASCO released *Shaping the Future of Oncology: Envisioning Cancer Care in 2030*, which presents a long-term vision of cancer care and outlines potential barriers. This report identifies three key drivers of change that are likely to have the biggest impact on cancer care over the coming decades:

1. "Big data." Rapid advances in health information technology (HIT) have created unprecedented opportunities to collect, analyze and learn from vast amounts of real-world data.
2. Cancer panomics. We are coming to understand the complex networks of molecular pathways and characteristics of the tumor microenvironment that interact to drive cancer and will need to be targeted, in combination, to develop prevention strategies and curative therapies.
3. Delivering value. Unsustainable cost increases and improvements in quality metrics are leading to a growing focus on cost effectiveness and "value" in health care.

Since issuing these reports, ASCO has worked with partners to drive the report's recommendations forward. Many other major stakeholders, including the National Cancer Institute (NCI) and the FDA, have also launched initiatives that will contribute to achieving the vision. Together, these steps represent significant new momentum toward a research system that realizes the potential of precision medicine.

We must reinforce these efforts by reexamining the traditional processes and assumptions in the development and delivery system, especially as we transition to an era where molecularly targeted agents will become increasingly more common. Inefficiencies in the clinical trial process exist and must be resolved at many levels: among the research community, providers, payers, at the National Institutes of Health (NIH) and the FDA. As a community, we need to rethink the way that safety is assessed in trials

of molecularly targeted treatments. To address this and other issues, ASCO is developing recommendations on modernizing eligibility criteria for clinical trials. With respect to pediatric cancer research, trials of promising new agents need to begin sooner and incentives need to be realigned. Currently, most pediatric cancer trials start only after completion of the adult pivotal trial. In order to speed drugs to children, trials should begin while the adult trials are ongoing. In addition, the pediatric patent extension program needs to be revisited. Currently, the program extends the patent of a drug if it can be used for the same disease in children. Children often do not suffer from the same diseases as adults, but we are discovering that some of the molecular targets of adult and pediatric cancers are the same. The patent extension should apply to drugs that can treat effectively pediatric cancers, even if it is not the same cancer as the adult indication.

We support the development of truly superior treatments. In March 2014, ASCO released a perspective, *Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes*, which calls on the community of patients, patient advocates, and clinical investigators to collectively raise the bar in our expectations of the benefits of new therapies and to design clinical trials to demonstrate greater benefits. It outlines goals for cancer clinical trials in several diseases that researchers should aim for, and patients should expect. The recommendations provide examples of "clinically meaningful outcomes" for advanced pancreatic, lung, breast, and colon cancers.

To accelerate progress, we suggest that you hold a roundtable discussion focused on oncology. Given the nature of the disease and the nation's longstanding investment in cancer research, the field of oncology has already dealt with many of the issues that have now begun to arise in other disease areas. An examination of what has worked, and what hasn't, would likely benefit your initiative.

Thank you for the opportunity to provide input. We look forward to working with you on the 21st Century Cures Initiative and offer ASCO as a resource to you.

Sincerely,

Clifford A. Hudis, MD, FACP
President
American Society of Clinical Oncology

ACCELERATING PROGRESS AGAINST CANCER

ASCO's Blueprint for Transforming Clinical and Translational Cancer Research

NOVEMBER 2011

ASCO®
American Society of Clinical Oncology

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Imagining the Future: A Patient's Experience

You visit your doctor for your annual physical. She asks you to undergo a routine blood test. You wait a few minutes for the test to process and are called back to hear the results. She tells you that the test detected cancerous cells in your bloodstream, which are an indication of an early-stage cancer that is developing somewhere in your body.

The doctor reassures you that since the cancer was detected at a very early stage, there is a good chance that it can be managed or cured. She refers you to an oncologist and recommends additional tests to determine the molecular "fingerprint" of the cancerous cells. This takes just a few hours, and will provide vital information about the gene and protein abnormalities that may be driving the cancer.

When you meet your oncologist, he tells you that you have an early-stage cancer arising in the kidneys. But the tumor's location isn't really what he considers most important. In this molecular era of cancer treatment, what matters most is your genomic profile and the unique combination of molecular features of your cancer. In your case, the cancer is caused by a specific set of abnormal genes, which are disabling three key "hubs" in the vast network of molecular pathways that regulate the growth of your cancerous cells. As a result, the cells have become stuck in an "always grow" mode.

Your oncologist explains the standard treatment options available to target these hubs. He also notes that your electronic health record (EHR) indicates that based on your medical history and genomic predisposition — and on information from other patients like you who have undergone these treatments — you will probably have an adverse reaction to one of the standard therapies. The EHR also identifies a clinical trial of a new therapy, for which you qualify based on your molecular profile.

Your oncologist explains the risks and benefits of participating in the clinical trial, and you go home to think it over

and talk with your family. You review your EHR lab report and other personalized information on your computer and contact your local comprehensive cancer center's second opinion service to review your options. With the second opinion confirming your doctor's assessment, and feeling confident in your own knowledge, you return to your oncologist's office, enroll in the trial, and immediately receive electronic confirmation with information on next steps.

The treatment being studied in the trial includes two new drugs, which are attached to a microscopic "nanoparticle shuttle" that will deliver them directly to individual cancer cells, sparing healthy cells and minimizing side effects.

You also receive a saliva reader that plugs into your smart phone, together with a few mobile applications that allow you to record your symptoms during the trial and send information automatically to your EHR. Every eight hours, your phone will buzz to remind you to take your medicine and answer a short series of questions about how you're feeling. It alerts you that you should expect to be slightly fatigued and includes suggestions for managing this side effect.

The next day, a nurse calls you to make sure everything is working properly and to answer any questions. He tells you he will be monitoring your progress throughout the trial, and will contact you if the answers you provide indicate anything out of the ordinary. He also reminds you that all of your doctors — including your primary care physician and cardiologist — will be able to track your status through your EHR, so they can continue to make fully informed decisions about your other health care needs.

You feel reassured because your doctor and nurse know a great deal about the drivers of your cancer, and are helping you make informed decisions to manage your cancer while continuing to work and live an active life.

INTRODUCTION
A New Vision for Clinical and Translational Cancer Research

"We can no longer think of cancer as one disease. Even something like lung cancer could be hundreds of distinct cancers, each defined by specific molecular characteristics requiring different treatment approaches. This makes research more challenging, but the payoff for patients will be enormous."

MICHAEL P. LINK, MD, PRESIDENT OF ASCO

It has been 40 years since President Nixon signed the National Cancer Act into law.[1] With this landmark legislation, the United States entered an era of rapid advancement in our understanding of cancer and our ability to prevent, detect and treat it. As a result, more people are surviving cancer than ever before, and quality of life for those with the disease has dramatically improved.[2]

While advances have been extraordinary in many ways, there is an urgent need to accelerate the pace of progress. Many cancers are not detected until their latest stages, and others have resisted most attempts at treatment. As a result, cancer still kills more than 500,000 people in the United States each year[3] and the disease is projected to become the nation's leading killer over the next decade as the population ages.[4] Worldwide, the cancer problem is growing quickly.[5]

With recent breakthroughs in technology and in cancer "panomics" — the combination of genes, proteins, molecular pathways and unique patient characteristics that together drive the disease — there is new hope and unprecedented opportunity to make more rapid advances. Yet our nation's translational and clinical research system is unprepared to deliver on this promise.

This report from the American Society of Clinical Oncology lays out a vision for an approach to clinical and translational cancer research that takes full advantage of today's scientific and technological opportunities. If bold action is taken to achieve this vision, we can realize major new advances in cancer prevention, detection and treatment and improve the care of patients.

The report makes the following case for action:

- **Investments in cancer research have already saved and improved countless lives.**
  While cancer has proved far more difficult to defeat than imagined when the National Cancer Act was enacted, today, two out of three people live at least five years after a cancer diagnosis, up from roughly one out of two in the 1970s. The nation's cancer death rate has dropped 18 percent since the early 1990s, reversing decades of increases.[3] And people with the disease are increasingly able to live active, fulfilling lives, due to better management of symptoms and treatments with fewer side effects.

- **Cancer science is in a period of revolutionary change.**
  As a result of our rapidly growing understanding of the biology of cancer, treatments are increasingly targeted to the molecular "triggers" that cause normal cells to become cancerous. Researchers are using new technologies — from the fields of computational chemistry, imaging technology, nanotechnology, health information

technology and genetic engineering – to engineer therapies that target the multiple pathways that combine to drive a patient's cancer, with hundreds of potential new targets yet to explore.

- **Clinical cancer research and patient care could be vastly more targeted, more efficient and more effective.**
  With recent advances, it is not unrealistic to imagine that over the next decade, clinicians will increasingly be able to choose therapies that target the characteristics of each cancer and each patient. In addition, cancer diagnosis will be earlier, and diagnostic tests will provide molecular information that informs treatment decisions and management of side effects. A growing number of effective treatments will be targeted to defined patient populations. And new drugs will be developed simultaneously with the diagnostic tools that are needed to guide their use.

  Treatments will be targeted not only at cancerous cells but also at pre-cancerous cells and the cell's surrounding environment. Clinical trials will be launched and completed far more quickly. Every patient will have the opportunity to contribute to translational and clinical research thanks to advances in health information technology (HIT) that enable real-time collection and sharing of clinical information through electronic health records (EHRs).

- **But this vision is possible only if we transform the way translational and clinical cancer research is conducted.**
  The nation's cancer drug development and clinical research infrastructures have not kept pace with recent advances. The clinical trials system has been weakened by a labyrinth of regulatory requirements and years of under-funding. Traditional trial designs and drug development models are insufficient to fully capitalize on the potential of molecularly-targeted therapies. And companies are discouraged from sharing ideas or testing promising new treatments in combination due to a lack of incentives and the absence of a clear process for collaboration.[6, 7]

Explore 40 Years of Progress in Cancer Research: ASCO's CancerProgress.Net

In May 2011, ASCO launched CancerProgress.Net, a dynamic website that provides an interactive journey through four decades of advances in the prevention, diagnosis and treatment of cancer.

Created to mark the 40th anniversary of the National Cancer Act, CancerProgress.Net was developed under the guidance of 17 of the nation's leading oncologists. Key features of the site include:

- An interactive timeline of cancer research advances – covering 14 different cancer types and every type of care, from prevention to molecularly targeted therapies
- "Data visualization" tools to help bring select cancer statistics to life
- Expert interviews and historical commentary from renowned leaders in oncology

- Downloadable slides and links to other resources

The site is updated regularly to feature major new advances in cancer research and patient care.

ABOUT THIS REPORT

This report from ASCO — which represents more than 30,000 physicians and other professionals who treat people with cancer and conduct clinical research — provides a high-level blueprint for transforming the translational and clinical cancer research system in the United States. It addresses three main areas in which changes are urgently needed:

1. **Establishing a new approach to therapeutic development,** driven by our more thorough understanding of cancer biology
2. **Designing smarter, faster clinical trials** that are appropriate for the era of molecularly-targeted therapies
3. **Harnessing information technology** to seamlessly integrate clinical and translational research and patient care, ensuring that every patient's experience can inform research and improve care

In each area, we describe the vision that ASCO believes can become a reality within the next decade and provide an initial blueprint for action.

We also outline the steps ASCO plans to take to achieve this vision, and we invite stakeholders in the cancer research community (e.g., policymakers, patient advocacy organizations, professional societies, public and private research sponsors and regulatory bodies) to join us. Over the next three years, ASCO will work with partners throughout the cancer research community to develop more detailed plans of action for each of the three areas covered in this report.

ASCO'S BLUEPRINT FOR ACTION

I. A NEW APPROACH TO THERAPEUTIC DEVELOPMENT

THE SITUATION TODAY

For decades, the development of new treatments for people with cancer involved choosing drugs for tumors based largely on their location within the body. Today, thanks to genomic advances and a deeper understanding of cancer biology, this approach is being replaced with development of approaches that target specific molecular characteristics of the cancer cell – the molecular "on-off" switches that are critical to driving cancer cells' uncontrolled growth.

This targeted approach has already improved treatment for many cancers, especially those that are driven by a single powerful mutation. One of the best-known examples is breast cancer that over-expresses the HER2 protein. Once one of the most difficult cancers to treat, this form of breast cancer is now highly treatable, thanks to the development of drugs that specifically block the cancer-fueling effects of HER2.[8]

For the vast majority of cancers, however, it has become increasingly clear that targeting a single molecular defect is not enough. Most cancers are driven by multiple mutations that provide pathways for cancer development, many or all of which may need to be targeted for the cancer's growth to be prevented or controlled. In addition, cancers that are ostensibly of one type – for example, lung cancer – can be driven by many different molecular defects and require very different treatments. In short, there is no single breast cancer or lung cancer or colon cancer, but rather several or even dozens of molecularly distinct cancers of each type that can arise.

While our understanding of this molecular basis for cancer is growing rapidly, our current approach to developing and testing new therapies is ill-equipped to capitalize on that new knowledge:

- While new technologies are allowing us to decode the genomes of a growing number of cancers, researchers have a limited understanding of which molecular pathways within a person's cancer are most important to target.

- Researchers also have a limited understanding of how the cancer cell's environment – for example, the molecular characteristics of the surrounding tissue – influences the cancer's development and spread.

- We do not have proven, easily detectable and measurable biomarkers (see box, p. 8) to identify patients based on the molecular characteristics of their cancer, or to monitor the effectiveness of prevention and therapeutic strategies in real time.

- With molecularly targeted treatment and prevention strategies, more information about each patient's cancer is needed to identify the patients who are most likely to benefit from a given treatment. To realize the greatest potential benefits, development of treatments should be accompanied by development of diagnostic tests to identify appropriate patients and monitor the outcomes of those treatments in real time. Today, however, treatments and diagnostics are not typically developed and tested at the same time. An additional complication results because therapies and diagnostic tests are regulated by different government bodies.

- Currently there is no consensus among researchers or research funders about the most urgent and promising priorities for therapeutic and diagnostic

Biomarkers and Their Functions

Biomarkers are substances or biological features arising in tissue, blood or other bodily fluids that can be easily identified and used to diagnose or monitor a disease and its response to treatment. In practice, biomarkers are detected through various diagnostic tests — for example, blood or saliva tests, or imaging tools such as CT scans or magnetic resonance imaging (MRI).

Perhaps the best-known example of a biomarker is cholesterol level in blood, which serves as a marker for heart disease. Because of the strong link to heart disease, monitoring cholesterol in blood is an effective way to determine the effects of anti-cholesterol medications on reducing the risk of heart attacks.

In cancer, biomarkers will increasingly serve several important functions. More and more, they will determine if a person is at increased risk for certain cancers; enable physicians to diagnose some cancers at an early stage; and guide treatment decisions.

In cancer research, biomarkers are increasingly essential to identify new treatment targets; quickly identify patients who are eligible for specific trials; and monitor responses to therapy.

Current examples of cancer biomarkers include:

- CA125 for monitoring response to ovarian cancer treatment[9]
- Tumor glucose metabolism, as measured by PET imaging, to provide a more accurate prognosis[10]
- HER2 gene expression to determine the likelihood of benefitting from targeted breast cancer drugs such as trastuzumab (Herceptin) and lapatinib (Tykerb)[8]

development. As a result, there is widespread duplication of effort in some areas, including "me-too" trials of therapies. In addition, trial sponsors often focus on areas that are unlikely to result in major advances over existing options, while critical gaps in cancer prevention and treatment are left unaddressed.

- With multiple molecular triggers for each cancer, it is likely that a combination, or "cocktail" approach to treatment and prevention strategies will be required. Yet legal, financial and regulatory hurdles currently make it challenging for companies to work together to test promising combinations.

- Combining different strategies for prevention and treatment of cancer will require teams of researchers. Academic incentives, however, reward individual research efforts over team approaches.

ASCO'S VISION FOR THE NEXT DECADE

Within the next decade, ASCO envisions increasing reliance on molecularly-driven, collaborative approaches to cancer diagnostic and therapeutic development. Development of new treatment and prevention strategies will be governed primarily by the molecular characteristics of the cancer, rather than its location in the body. New, more collaborative research models and trial designs will enable testing of multiple drugs at once, and provide more meaningful insight into what does and doesn't work, and why. Physicians and researchers will have a robust set of biomarkers to guide prevention, diagnosis and treatment decisions for many more types of cancer. And new technologies will open the door to entirely new approaches to cancer prevention, detection and treatment.

The key elements of ASCO's vision are as follows:

Defining Cancer Based on Characteristics, Not Solely by Location in the Body

Cancer will no longer be identified primarily by the location in the body where it begins, but also by its

panomic characteristics — the complex combination of patient-specific molecular characteristics that drive the development and behavior of each cancer. Specifically, over the next decade:

- Researchers will decode the genomes of a large inventory of cancer types. This will include characterization of cancers at the earliest stages, as well as the cells that surround the cancer as it arises and spreads — the "cancer environment" — so that researchers can better understand the entire spectrum of biological changes that occur in the development of cancers.

- Researchers and clinicians will have the tools to quickly conduct a panomic analysis for every patient with cancer. This analysis will include an examination of the patient's genomic makeup and a complete molecular characterization of their cancer cells.

- In combination, this information will provide a more sophisticated view of the cancer's development — and how to prevent, halt or reverse it. Researchers and clinicians will identify the series of critical molecular "hubs" that must be targeted simultaneously to shut down the entire "power grid" that drives the cancer cell's development and growth.

Molecularly-Driven Diagnostic and Therapeutic Development

Our expanded knowledge of cancer- and patient-specific molecular characteristics will help transform the approach to diagnostic and therapeutic development over the next decade:

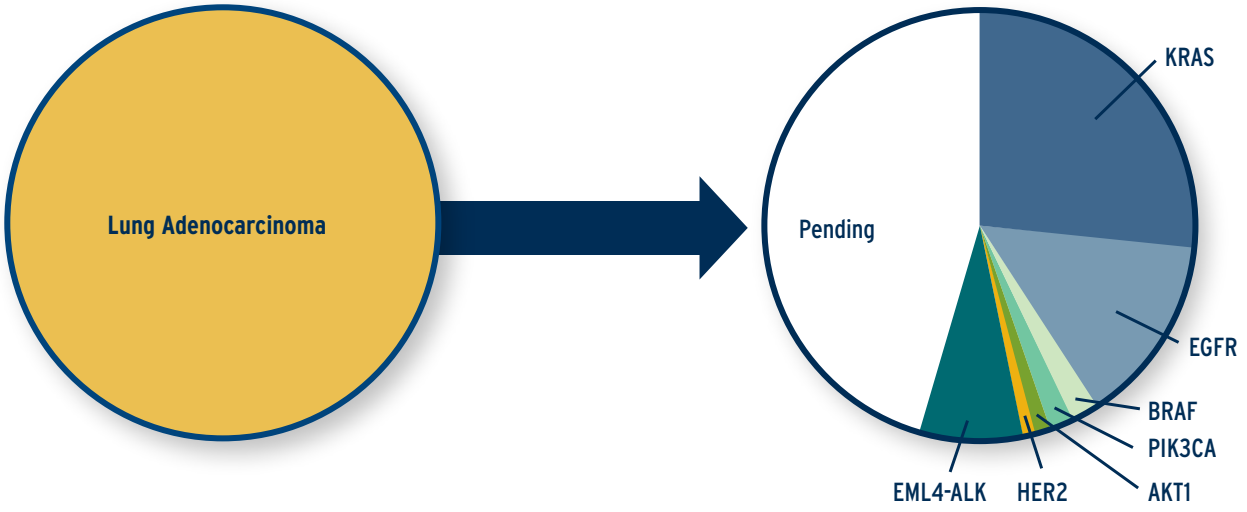
- Cancer treatment and prevention therapies will increasingly target the key molecular hubs that drive cancer growth — not just individual mutations. This will enable treatments to become much more personalized, taking into account when and how to intervene to hit the right targets in a given tumor, and how treatments are likely to affect each patient.

- Experts from a wider range of professional

Cancer in the Molecular Era: Identifying the Drivers of Lung Cancer

BEFORE: One Disease

TODAY: Many different forms of lung cancer driven by different molecular defects — with more yet to be identified

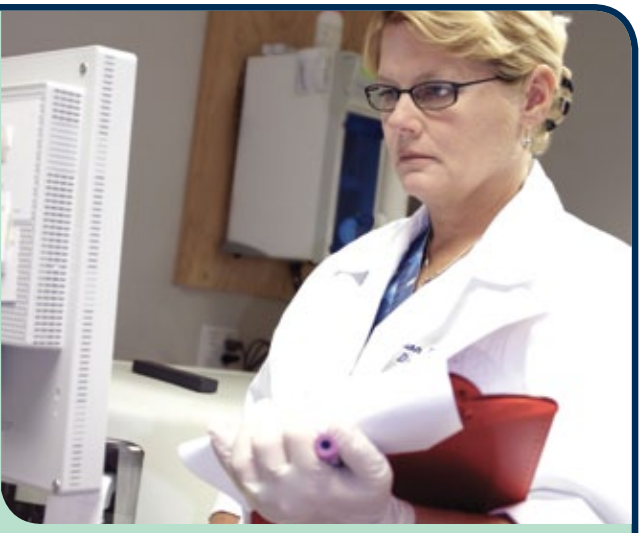


FUTURE ONCOLOGIST PERSPECTIVE
Therapeutic Development

ASCO envisions that in a decade, the following experience will be routine:

We used to have to figure out the best treatment for a patient just by looking at the tumor under a microscope and assessing the patient's symptoms. That was like trying to fix a car by looking at the engine and listening to it idle. Now, we have the tools to take apart the engine and address the specific problem. With a fast blood test, I can find out what is driving my patient's cancer so that we can find the right treatment.

We can do this now because of decades of hard work studying the molecular engines of many different cancers, and it's been a real blessing to my patients.

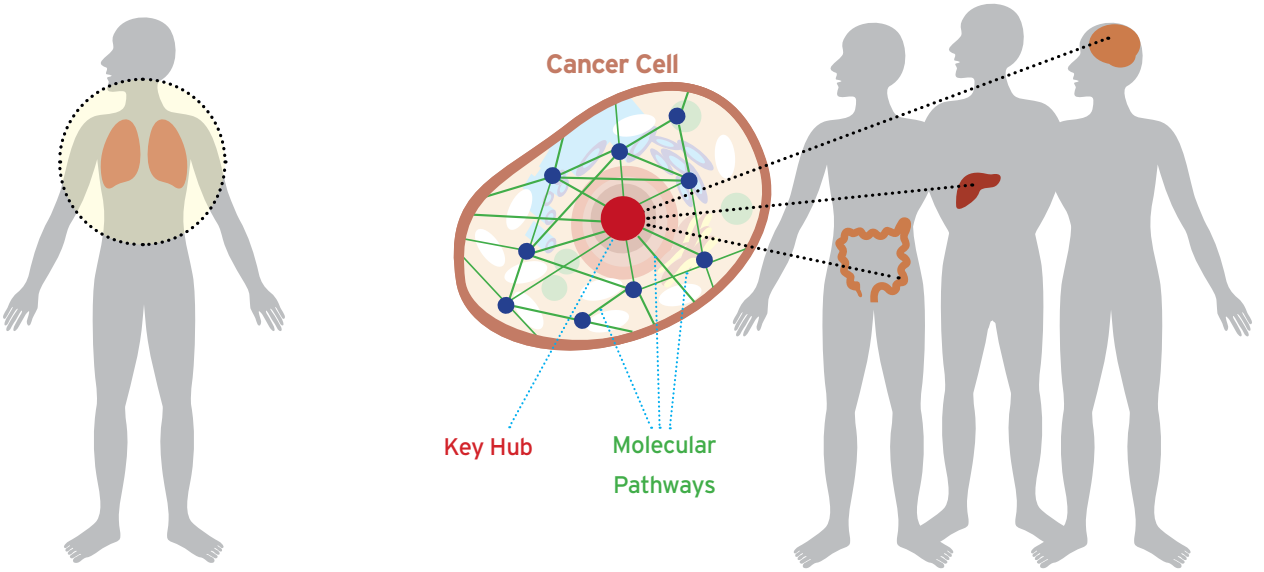


We don't have to go through multiple rounds of therapy and use a hit-or-miss approach with drugs that have awful side effects. We have greater assurance at the outset that we're choosing a drug that will work and that we are using a dose that is likely to be effective and minimize side effects.

A New Model for Therapeutic Development

OLD MODEL: Treatment is determined by a tumor's location in the body, without regard to the molecular charateristics of the patient or the tumor.

NEW MODEL: Treatment is determined by key molecular "hubs" that must be targeted within the cells, and is only administered to patients whose tumors are found to have those hubs – potentially without regard to the tumor's location in the body.



disciplines will collaborate on the development of innovative cancer treatment and prevention strategies, and new strategies will incorporate a greater variety of approaches. Already, for example, materials scientists and chemical engineers are helping to design new mechanisms to target cancer cells and avoid normal cells.

- Clinical trials will routinely collect information directly from participants to help determine how and why investigational therapies affect patients differently. This patient-reported data, including real-time reports of symptoms and other patient experiences, when combined with more complete information about the genetic make-up of their cancers, will help guide future research.

- Regulatory agencies, trial sponsors and researchers will begin discussions early in the therapeutic development process, enabling faster review and approval of new treatments and diagnostics. Together, regulators and researchers will develop new processes and decision-making tools to more effectively monitor, collect and incorporate data on effectiveness and potential side effects of different types and combinations of new treatment and prevention strategies.

More Robust Biomarkers

Over the next decade, ASCO envisions that researchers will identify and validate many new biomarkers (see box, p. 8) that can be used to help prevent cancers, detect cancers earlier, match patients with effective treatment and prevention strategies at the right doses, monitor clinical benefit and predict long-term outcomes. The availability of these new biomarkers will also accelerate research by helping to identify useful drug targets and patient populations most likely to benefit, and to more effectively monitor the impact of investigational treatments in trials:

- New devices will be able to rapidly analyze many potential biomarkers at the same time, allowing researchers to more quickly and easily identify those that can guide research and patient care.

FUTURE INDUSTRY PERSPECTIVE
Therapeutic Development

ASCO envisions that in a decade, the following experience will be routine:

With so much more known about cancer biology, thanks to a lot of collaborative work with other companies, NCI, and foundations, drug companies are now able to make better tools for doctors to use. It's great to be working together with other companies and these stakeholders in the early stages of drug development, to build knowledge we can all use in our research.

In the old days, it was like having only one tool to do all your home repairs — if it worked for removing the drywall it probably wouldn't work for the plumbing. Now, we are able to look at the entire molecular system that drives a specific cancer and design the tools needed to specifically fix each part of the system.

And we're not just developing drugs — we've also been working with engineers and materials scientists to come up with all kinds of new devices to detect and attack cancers. This cuts down on side effects and allows doctors to individualize the treatment based on the individual person and their cancer.

It's much more rewarding to develop these more comprehensive treatments than it was to work on drugs that would just attack one piece of the problem and increase life span by only weeks or months.

- Biomarkers and diagnostic assays will be developed and validated simultaneously with new cancer treatments — not as separate steps in the development process as they often are today. This will shorten the time before patients can benefit from new treatments, by accelerating the availability of diagnostic and monitoring tools that are required to guide the use of new therapies in the clinic.

- Advances in imaging technologies will expand the range of imaging options that can be used as biomarkers. This will provide faster and less invasive ways to detect and monitor cancers.

- New biomarkers will help to better define and quickly identify the patient populations for specific clinical trials, by allowing widespread, rapid screening for specific genetic mutations and other molecular features of the cancer.

- New biomarkers will enable expanded use of current therapies to new tumor types that share key molecular features. In a limited number of cases, this is already occurring. For example, trastuzumab, a treatment developed to target HER2 in breast cancer, has shown promise for gastric cancer that overexpresses the same protein.[11]

New Methods of Cancer Prevention, Diagnosis and Treatment

Over the next decade, new technological advances will open the door to entirely new methods of preventing, diagnosing and treating cancer:

- Advances in materials science will allow researchers to aim therapy directly at the physical tumor site, increasing effectiveness and decreasing side effects. For example, refinements in the use of microscopic "nanoscale" technologies may better and more safely deliver drugs to their precise target.

- Tools will be developed to identify "circulating tumor cells" that have detached from a tumor and are traveling in the bloodstream. These cells may be used to detect cancer, measure the effectiveness of treatments and monitor for cancer recurrence, without more invasive techniques.

- A greater understanding of biology, together with new technologies, will allow researchers and clinicians to identify and eradicate cancer stem cells — a class of cells that gives rise to other forms of cancer cells, and are thought to be the most critical to attack in order to stop cancer's spread and recurrence.

- Thanks to improved understanding of both the genomics of cancer and tumor cells' interaction with the rest of the body, researchers will be able to develop new immune therapies to harness the body's own ability to seek out and destroy cancer cells.

RECOMMENDATIONS

ASCO recommends that the following actions be implemented over the next three years to accelerate therapeutic development and make this vision a reality:

Establish clear priorities for therapeutic and prevention strategies and biomarker development: Identify and prioritize the targets that are most urgently needed to advance cancer patient care, and the biomarkers that will be essential to guide the use and measure the effectiveness of resulting therapies.

- ASCO will partner with other medical and scientific professional societies and the National Cancer Institute (NCI) — building on NCI's existing "Provocative Questions" project[12] — to convene a series of workshops with basic, translational and clinical researchers, industry, the Food and Drug Administration (FDA), patient organizations and other stakeholders to:
  1. Identify and prioritize the most promising molecular pathways to be targeted.
  2. Identify new opportunities and approaches for biomarker development.
  3. Identify effective strategies to improve research on new methods and combinations of cancer prevention and treatment approaches.

Incentivize collaboration in therapeutic development: To support more efficient development and evaluation of combined therapies and biomarkers that will be central to the future of cancer care, medical societies and cancer research advocates should evaluate the need for financial and regulatory incentives to ensure that industry and researchers can pursue the most urgent priorities. Mechanisms for "pre-competitive" collaboration among companies, researchers, and government and philanthropic research sponsors should also be explored, particularly for the development of new biomarkers. The process of biomarker discovery and validation is complex, and requires networks of investigators capable of open, intensive interactions, as well as substantial funding support.

- ASCO will collaborate with partners at NCI and the Institute of Medicine (IOM) to convene a working group with industry, academia and other federal agencies to:
  1. Explore ways to promote a more collaborative approach to developing new prevention and therapeutic strategies. This discussion would seek to develop a strategy that lowers the consequences of failure to enable academic researchers and companies to become more innovative.
  2. Develop consensus on whether modifications are needed to intellectual property law to facilitate and incentivize collaboration.
  3. Develop recommendations and a strategy to create a clear pathway for regulatory review and oversight of diagnostic tests that relate to use of biomarkers and therapies.

- ASCO applauds National Institutes of Health (NIH) and NCI efforts to encourage collaborative research between academic and community research centers.[13, 14] ASCO encourages NIH and NCI to continue to implement these types of changes. As part of the grants review process, NIH and NCI should also provide credit to research projects that involve a multidisciplinary, collaborative approach.

II. FASTER, SMARTER CLINICAL TRIALS

THE SITUATION TODAY

Clinical cancer research — involving rigorous trials that test the safety and efficacy of new therapies in people — is the engine that drives progress against cancer. Clinical trials are the only way to translate cutting-edge laboratory discoveries into treatments that extend and improve the lives of patients. Four decades ago, the National Cancer Act led to major new U.S. investments in clinical cancer research. Since that time, clinical trials have yielded steady advances in our ability to treat, detect and prevent cancer, and have helped to significantly extend patient survival and reduce mortality.

While progress has been substantial, it has generally been the result of incremental advances over time. Today, the remarkable pace of scientific and technical change is opening the door to more rapid advances. Yet our nation's clinical research system is poorly equipped to realize today's scientific potential, and is in desperate need of modernization and repair:

- Research sponsors currently devote substantial resources to trials and therapies that promise only marginal improvements over current standards of care. In part, this is due to a lack of clear priorities or a shared understanding of what constitutes meaningful advances in patient outcomes.

- It can take up to five years to develop and initiate a cancer clinical trial, and the time to complete trials has increased steadily as a result of overlapping regulatory requirements and complex data reporting.[6]

- Low patient and physician participation rates lead to delays in completion or even cancellation of trials. It is estimated that less than 5 percent of adult cancer patients participate in clinical trials, due to factors including extensive "exclusionary criteria" (factors used to limit participation in a trial, in order to protect patients and ensure a statistically valid trial result), low physician and patient awareness, uncertainty about insurance coverage and other barriers.

- Opportunities to conduct faster trials are limited by the small number of measures of efficacy that are acceptable to regulators — measures such as overall survival (the proportion of patients alive after a given time period), progression-free survival (the period during which a patient does not experience any new tumor growth or cancer spread during or after treatment) and disease-free survival (the length of time a patient is in complete remission following treatment). Researchers and regulators have been slow to reach consensus on the meaningfulness of other endpoints that could provide faster conclusions about the value of new therapies, in part due to insufficient ways to measure and document patient improvement.

- We now understand that seemingly identical cancers can be amazingly diverse at the molecular level, so that only narrow subpopulations of patients may respond to a particular treatment. However, most clinical trials continue to use broad patient populations that include many people who are unlikely to respond to a targeted treatment because their cancer does not have the relevant molecular defects. This lowers the apparent effectiveness of investigational treatments and exposes patients to unnecessary side effects.

- Trials do not routinely examine important indicators

of patient benefit, such as quality of life, that could help guide regulatory approval and future treatment decisions.

- Stagnant federal funding of the NCI's Clinical Trials Cooperative Group Program in recent years (see below chart) has stalled vitally important research that industry has little incentive to conduct, including studies that combine therapies from different companies, test FDA-approved treatments against different cancers, compare the effectiveness of different treatments, address rare diseases with little market potential or examine new prevention strategies.[6]

- The United States is gradually losing its leadership position in clinical cancer research, as important trials move overseas in search of more trial participants, less burdensome regulatory requirements and lower-cost health systems.

ASCO'S VISION FOR THE NEXT DECADE

Over the next decade, ASCO envisions a clinical cancer research system that is guided by clear priorities and is flexible enough to pursue new scientific opportunities as they emerge. With innovative trial designs and consensus on research priorities, researchers will conduct faster, more efficient trials that apply available resources to the most urgent needs of people with cancer.

Major elements of this vision include the following:

- Researchers, industry, patient organizations and government agencies will reach broad consensus on research priorities that hold the greatest potential to improve patient care and address public health need. Trials pursuing those areas will be prioritized for funding by research sponsors.

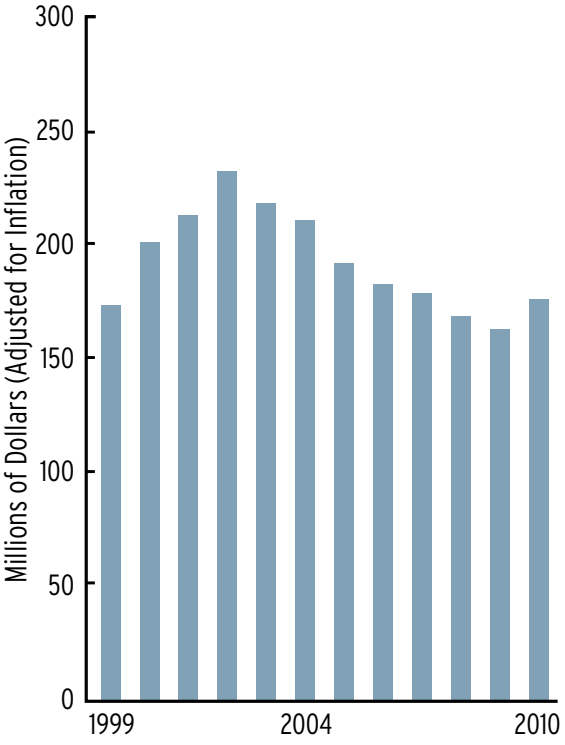
- As cancer biology is better understood, the criteria for participating in a trial will be based almost

The Central Role of NCI's Clinical Trials Cooperative Group Program

Most federally-funded studies of new cancer treatments are conducted under the NCI-funded Clinical Trials Cooperative Group Program. Through a network of more than 3,100 institutions and 14,000 researchers, the Cooperative Groups enroll more than 25,000 patients annually in cancer clinical trials and have made enormous contributions to the nation's progress against cancer.[15]

Cooperative Group trials have brought breakthroughs in adjuvant chemotherapy for breast and colon cancers, breast-conserving lumpectomy to avoid mastectomy (surgical removal of the breast) and new standards of care for blood cancers, brain tumors and many others.

Yet funding for the Cooperative Group Program has declined in real terms in the past decade, threatening this vital component of the nation's clinical cancer research system (see chart).



Source: ASCO
Data from the National Cancer Institute; inflation adjustments based on the National Institutes of Health Biomedical Research and Development Price Index

FUTURE RESEARCHER PERSPECTIVE
Clinical Trials

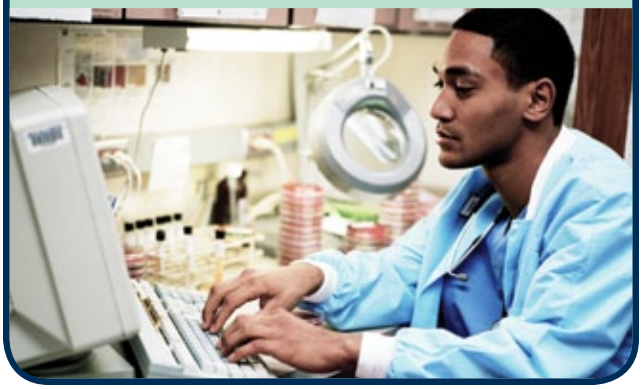
ASCO envisions that in a decade, the following experience will be routine:

Clinical trials are far more successful because we have a much better idea of what to look for and who to look for it in.

Our multi-talented teams can quickly take ideas from the lab to the bedside because we have biomarkers that allow us to measure a patient's response to therapy in a matter of weeks, not years.

We can also take the data from the clinic back to the lab and refine our trials or come up with entirely new ideas. This smooth back-and-forth allows us to zero in on what is driving the cancer. That means we can select patients who will be most likely respond, instead of testing a drug on everyone and trying to figure out why it works really well for only a few people.

And since we don't need as many people for any one trial, we can do more trials and develop more treatments faster. It's also easier to find people to participate, now that we have tools for patients to be more involved. Everyone who is interested can receive alerts when a suitable trial opens.

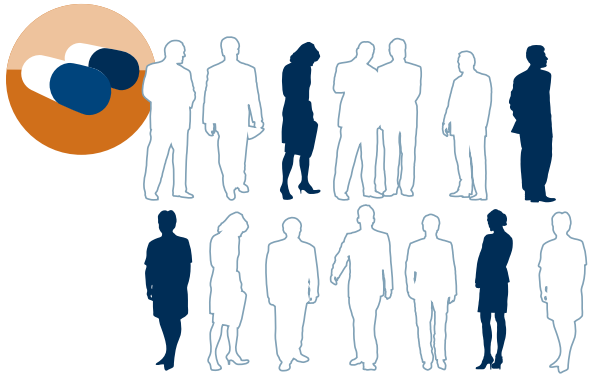


exclusively on the molecular characteristics of each patient's cancer. Trials will provide answers faster and more conclusively, because they will include only the participants most likely to respond to the treatment being studied.

- While researchers will need to screen larger numbers of patients to identify participants for each

Smaller Trials, Bigger Chance for Success

OLD MODEL: Large numbers of patients, not selected by molecular characteristics; lower chance of demonstrating effectiveness, since many participants do not have the molecular defects being targeted



NEW MODEL: Small patient populations, all with the relevant mutations or genetic defects; greater chance of desired results, since all participants have the potential to respond

trial, this task will be made easier through increased international collaboration between scientific and regulatory bodies. Such collaboration will enable researchers to more readily recruit patients from many different countries.

- Clinical trials will increasingly use adaptive designs that allow researchers to adjust a given study's population during the course of the trial, based on biomarkers that are found to be important as the trial proceeds. By ensuring that study populations consist of those patients who are likely to benefit, it will be possible to shorten the time that is required to complete trials and speed the development of new treatment and prevention strategies. Increased interaction between clinical, translational, basic science and health services researchers will enable ideas to flow more quickly from the lab to the clinic and back. Given the growing complexity of cancer science, a wider range of disciplines will be involved in the development of clinical and translational research concepts and protocols (e.g., materials scientists, engineers and epidemiologists).

- In addition to survival and anti-cancer response, therapeutic developers will routinely gather data on quality of life when testing new therapies in clinical trials. This will enable greater recognition of the value of a treatment based not only on patients' survival, but on the *quality* of their survival. The FDA and therapeutic developers will increasingly work together to enable consideration of these factors in approval decisions and to include this information on drug labels. This will provide clinicians and patients with more information about the benefits of approved treatments.

- ClinicalTrials.gov, the nation's registry of federally and privately supported clinical trials, will include more critical information in a useful format, such as information on initiated projects in early development and trial results. This more robust database will enable investigators to build on results of completed research, prevent duplication and help identify the most important research opportunities.

RECOMMENDATIONS

ASCO recommends the following actions be implemented over the next three years to modernize the way in which clinical trials are conducted and help to achieve the vision above:

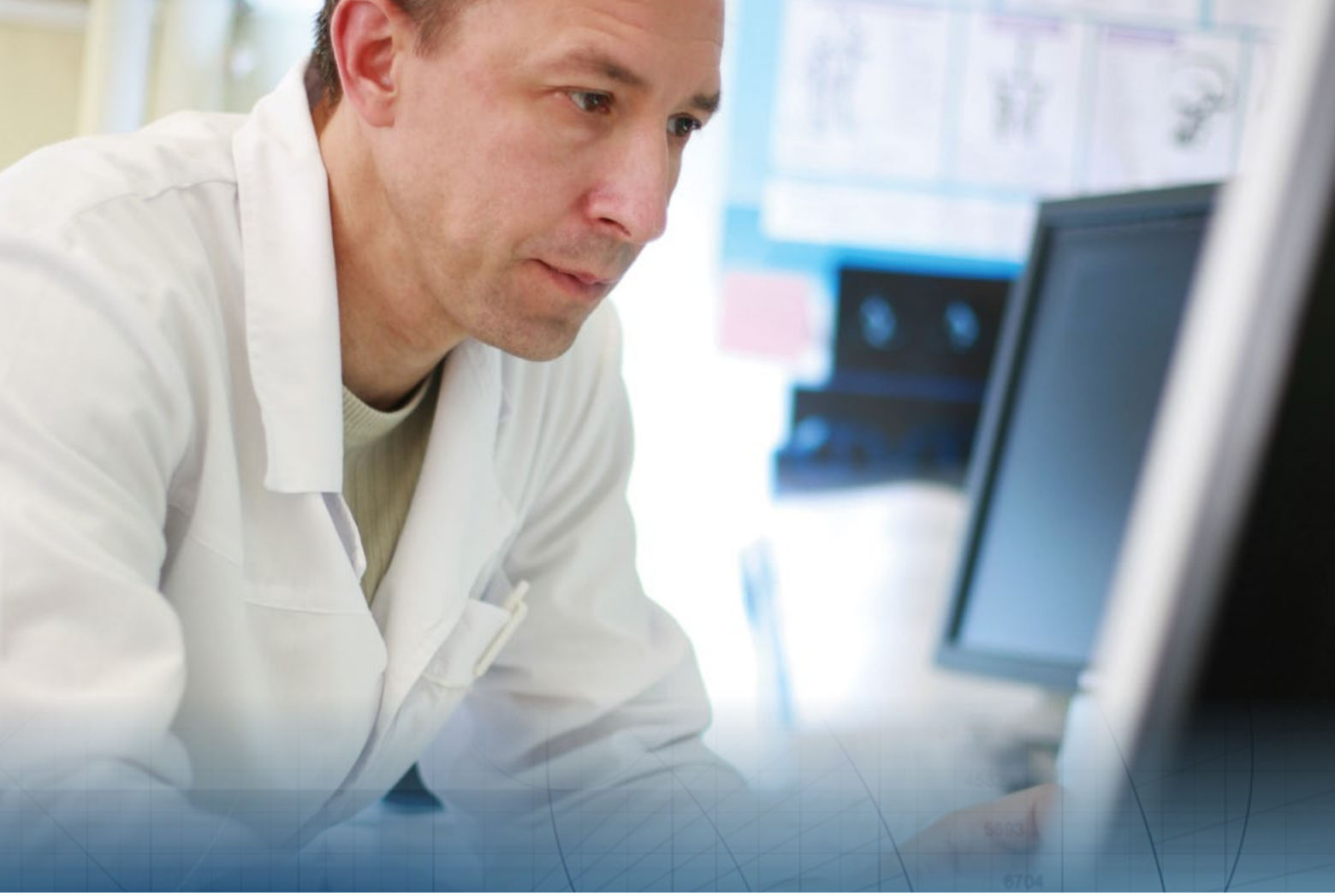
Prioritize trials with the greatest potential benefits for patients: The cancer research community should shift away from trials that promise only marginal improvements in care, and prioritize development of treatments, diagnostics and prevention strategies that represent significant advances for patients. Trials should focus on demonstrating meaningful patient outcomes, including both significant reductions in mortality and improvements in quality of life.

- ASCO will partner with patient advocates to convene a working group of experts in the field (including industry, investigators from multiple areas of biomedical research, NCI, FDA and insurers) to develop consensus on the specific benefits that constitute "meaningful patient outcomes."

- The working group will develop proposals to encourage broad adoption of meaningful patient outcomes – for example, working with insurers to ensure these outcomes are linked to eventual coverage of new treatments, and encouraging peer-reviewed journals and medical meetings to adopt policies that prioritize publication and presentation of trials that demonstrate such outcomes.

Select study populations based on molecular characteristics: To the greatest extent possible, clinical trials should be conducted in populations based on their molecular characteristics. At the same time, researchers should decrease use of other, less meaningful exclusionary criteria, such as having had prior cancers or having brain metastases. In addition, clinical trial populations should better reflect the racial, ethnic, age and gender diversity of people with cancer.

- ASCO will partner with NCI, Cooperative Groups and



industry to convene stakeholders in trial development to examine current exclusionary criteria and determine which criteria are scientifically required and which can be eliminated as we move more completely into the era of targeted treatment and prevention strategies.

Employ flexible, efficient trial designs: ASCO will bring together government agencies, academia and public and private trial sponsors to develop shared standards for new and flexible trial designs that allow researchers to achieve results efficiently with smaller, molecularly-defined sub-populations of patients. These new trial design standards should promote the use of surrogate study endpoints that represent meaningful measures of benefit to patients and will require less time to achieve.

- Building on past work with FDA and professional societies, ASCO will hold a state-of-the-science workshop on surrogate endpoints to catalog successful approaches, identify new standards and develop strategies to improve their use and promote their recognition by regulatory agencies.

- ASCO will create educational modules to enable researchers and biostatisticians to make greater use of innovative clinical trial designs.

Streamline data requirements for new uses of existing treatments: In regulatory applications for additional uses of already approved cancer drugs, FDA and industry should streamline data reporting by recognizing and building from the safety data that already exists for the treatment. Collection of new data should be focused only on those scientific questions that are directly relevant to clinical decision making. Such applications today require collecting information on known, low-grade safety risks and complete records of other medications being taken by individual study participants. However, these data do

not routinely inform regulatory or clinical practice decisions and consume significant time and resources.[16]

Train health care providers in clinical research: Medical societies and educational institutions should encourage and train cancer care providers to conduct clinical research as an integral component of patient care.

- ASCO will develop and disseminate educational modules and materials to teach core concepts of clinical research. These will be designed for use during training across all medical disciplines. The educational content will address the conduct of clinical research in both academic and community-based settings.

- ASCO will convene a working group with investigators and leaders from academic and medical institutions to discuss ways to recognize and reward physician participation in research, with a particular focus on team-oriented research.

Improve prioritization of NCI-sponsored trials: ASCO supports the efforts of NCI and the research community to prioritize NCI-sponsored clinical trials.[17] Policymakers and the research community should work together to increase support for high-priority, NCI-sponsored clinical trials while streamlining regulatory and logistical processes to expedite this vital research.[6]

- ASCO will partner with patient advocates, NCI, federally funded research institutions and industry to develop consensus on criteria for prioritizing cancer trials. The discussion should address the concepts of greatest public health need, meaningful patient benefit and scientific opportunity.

- NCI and private research sponsors should use these consensus criteria when determining which research to initiate.

Revitalize the NCI Cooperative Group program: ASCO will continue its partnership with stakeholders to ensure full implementation of recommendations issued by the IOM in April 2010 (see box).

Institute of Medicine (IOM) Recommendations to Revitalize the NCI Clinical Trials Cooperative Group Program

In April 2010, the Institute of Medicine (IOM) released its report, *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*. The report makes comprehensive recommendations to modernize and strengthen this vital component of the federally-funded clinical cancer research system, which has contributed many of the most important advances against cancer in recent decades.

The major IOM recommendations are as follows:

- Improve the speed and efficiency of the design, launch and conduct of Cooperative Group trials
- Incorporate innovative science and trial design into cancer clinical trials
- Improve the prioritization, selection, support and completion of trials
- Incentivize the participation of patients and physicians

Additional, detailed recommendations are made in each of these areas. (The full report is available at http://www.iom.edu/Reports.aspx.)

ASCO supports full implementation of the IOM report and is working with NCI, the IOM, Cooperative Groups, patient advocates and other stakeholders to advance key elements of the recommendations.

For information about ASCO's efforts, visit http://www.asco.org/GroupReorganization.

III. HARNESSING HEALTH INFORMATION THROUGH TECHNOLOGY

FUTURE PATIENT PERSPECTIVE
Health Information Technology

ASCO envisions that within a decade, the following experience will be routine:

It used to be that all my doctors kept separate records and I was the only one trying to track everything. Now that all my health care providers are using systems that communicate with each other, they can see and update my information on the same file. I can also review all my information (diagnosis, treatment options and side effects to expect) anytime I want on my smartphone. I can record how I'm feeling so that my doctors know what we should talk about before I arrive for my next visit, and they can call me between visits if there's something I should take care of myself — like taking fewer pills or picking up some medicine from the drug store.

I also receive important information electronically — last year I got an email when a clinical trial opened up that I qualified for, based on the information about my cancer in my EHR. My cancer doctor got the same message, so we talked about it at my next visit and I signed up. I had to go for treatment at a different location, and they pulled up my records and we were ready to go; no hours wasted filling out the same forms over and over again or retaking tests that I had already done. The EHR even updated my primary care doctor and my diabetes doctor.

THE SITUATION TODAY

Health information technology (HIT) has the potential to transform clinical cancer research and improve patient care. Yet this potential is only beginning to be realized.

New HIT tools are urgently needed to help synthesize the wealth of information that should inform patient care and research: physicians need better tools to help them stay abreast of rapidly evolving research and make increasingly complicated treatment decisions; patients need better tools to minimize the burden of coordinating their own care and to easily provide their doctors with information that could inform their care; and researchers need better access to clinical data and tissue samples to be able to identify research opportunities and emerging trends in real time.

Today, we are only beginning to develop the capability to process large amounts of data and use it to inform cancer research and care. This is due to several factors:

- Many health care providers are just beginning to use electronic health records (EHRs), which are key to securely collecting, analyzing and sharing patient information. In addition, standard formats for recording patient information are lacking, making it difficult or impossible to compare data from different providers or health systems for research purposes.

- There is no widely-used system that allows investigators to access information from EHRs for research purposes, while also protecting sensitive patient information.

- EHRs are not currently designed to alert patients and physicians to newly approved prevention methods, treatment options and clinical trials as they become available.

- Data on patient biospecimens (tissue and blood samples) is limited by the lack of standardized methods for biospecimen collection, storage, analysis and cataloguing. This limits researchers' ability to determine patient eligibility for clinical trials and to identify new research ideas.

- Debates about intellectual property rights and the limited availability of secure systems to ensure privacy of patient information limit the ability of patients to contribute biospecimens and information to inform clinical and translational research.

ASCO'S VISION FOR THE NEXT DECADE

ASCO envisions that within a decade, advances in HIT will make it possible to dramatically improve patient care and will allow researchers to draw upon the wealth of real-world patient and physician information to speed research. To help achieve this vision, ASCO is leading the development of a Rapid Learning System for Cancer Care, which will harness cutting-edge HIT to connect cancer patients, their health care providers and researchers to a central knowledge base; to synthesize information from millions of physician and patient experiences; and to deliver up-to-the-minute, personalized information that allows every patient to receive the highest quality care (see sidebar, p. 22).

Key elements of ASCO's vision are as follows:

- Researchers and clinicians will develop consensus on baseline demographic and treatment information to collect from all patients with cancer. HIT developers will build these standardized data fields into all EHR products. In addition, IT professionals will develop secure systems in which investigators can conduct health services and outcomes research without compromising patient confidentiality.

- Patient awareness of research will have increased thanks in part to novel strategies like online recruiting databases (see box, p. 23). Patients interested in participating in trials will be able to securely enroll in universal notification services that alert them when trials relevant to their cancer's molecular characteristics become available. Investigators will be able to use these notification services to send information to appropriate patients and clinicians when they launch a new trial.

- Access to real-time clinical data will greatly enhance insight into how patients respond to therapies and why. For example, it may help identify distinct groups of patients who are more likely to respond to a specific drug or are in need of other treatment options. These insights will help drive clinical research.

- All patients will have the option to contribute to clinical research by confidentially sharing information from their EHR for research purposes. A secure HIT environment will enable patients to permit their clinical information to flow securely and freely among oncologists, primary care providers and researchers.

- Patients and clinical trial participants will be able to access a secure portal where they can enter information about symptoms, side effects and health status in real time. This information will not only provide their oncologists with information needed to quickly resolve the patient's symptoms, but will also provide more detailed, reliable information for researchers about the real-world benefits and complications of treatments.

- Data obtained from biospecimens will be electronically linked in a secure environment to patients' clinical information, allowing physicians to easily explore relationships between the molecular characteristics of a patient and their cancer — in order to choose the best treatment, as well as identify the most promising clinical trial opportunities. In addition, researchers will be able to use information in a

secure way to test hypotheses. This will also enable a wide range of research from population-level effectiveness modeling to quality improvement and monitoring for the safe use of approved treatments.

RECOMMENDATIONS

In order to accelerate research and improve cancer care through health information technology, ASCO recommends the following actions be implemented over the next three years:

Standardize oncology EHRs: ASCO will continue its work with clinical, research and HIT stakeholders to define the functional requirements and clinical and research data elements needed for HIT products. The elements should include:

- All relevant information in a consistent format, including the cancer's molecular characteristics, site and prior treatments received by the patient.

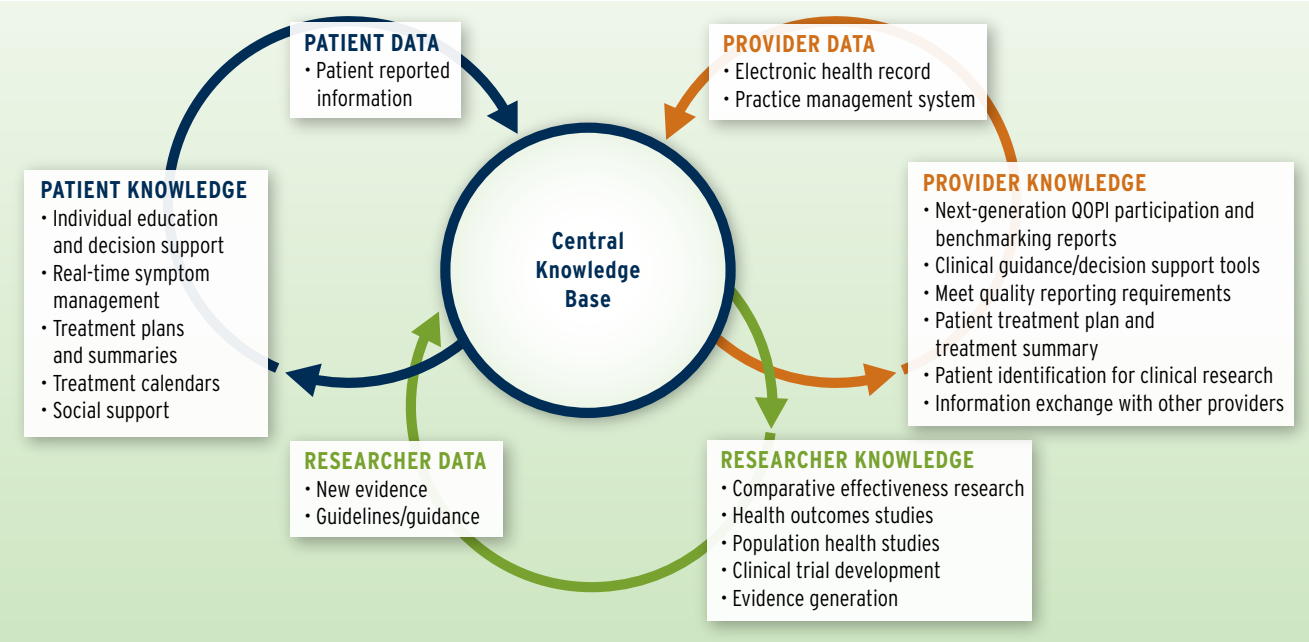
- Information from ClinicalTrials.gov about available clinical trials and eligibility standards. This will ensure that physicians and patients are alerted to clinical trials that may apply to the patient as they become available.

ASCO's Rapid Learning System for Cancer Care

This innovative, HIT-enabled rapid learning system environment will help to improve the quality of cancer patient care and accelerate research by forming a continuous cycle of learning: capturing evidence-based guidelines, evaluating quality of care against those recommendations, and creating insights through analysis of data from every patient experience.

To advance research, in particular, the system will:

- Provide a secure way to generate understanding of the outcomes of cancer patients. This will provide the research community with an unparalleled, high quality dataset to speed research
- Empower patients by providing personalized information, including clinical trials for which they are eligible based on their cancer type



- The ability to transfer data between clinical trial databases and patients' medical records to avoid discrepancies.

- Standardized fields for entering information about biospecimens, to help facilitate treatment decisions, determine patient eligibility for clinical trials, and ensure that researchers can analyze and draw conclusions from larger numbers of patients.

- Secure web-based and mobile applications that allow patients to provide information about symptoms and health status at any time.

- Terminology standards for demographic information and treatment outcomes that allow researchers to more effectively conduct health services and outcomes research.

Build ASCO's Rapid Learning System for Cancer Care: To make this groundbreaking system a reality, ASCO is working with partners in the cancer, research and informatics communities to:

- Transform ASCO's Quality Oncology Practice Initiative (QOPI®) into a fully electronic system (http://qopi.asco.org). QOPI is the first and only nationwide system to help oncology practices monitor and improve the quality of care they provide. Once the system becomes fully electronic, practices will be able to share data in real time, enhancing insight into patient outcomes, improving quality and helping to inform clinical research questions. The continually expanding QOPI measures will be a core component of ASCO's Rapid Learning System for Cancer Care.

- Develop standards, applications and methods for collecting patient-reported outcomes (i.e., symptoms, side effects or quality of life indicators) in clinical care and clinical trial settings, as well as methods for notifying patients and doctors of relevant clinical trials.

- Partner with HIT developers to provide patients and physicians with the most up to date information and tools to guide decisions.

Using HIT to Increase Patient Involvement in Research

Several innovative HIT-based registries are helping to increase the number of people available for participation in cancer clinical trials. Examples include:

- **Love/Avon Army of Women:** An online registry working to recruit one million women willing to participate in breast cancer research. Women with and without breast cancer share contact information and basic demographic details, and agree to be contacted when new studies open. They are emailed when a new study becomes available, and are asked to respond if they are willing to participate. This approach has dramatically accelerated patient recruitment for some research studies — in one case, recruiting as many women in 10 months as it would have taken 3 years to recruit using a full-time recruiter (http://www.armyofwomen.org).
- **ResearchMatch.org:** An NIH-funded online registry for healthy individuals willing to take part in clinical research studies. Individuals fill out an online form, including basic health data. Researchers are able to search confidential volunteer data through the ResearchMatch website, and send a message to individuals who are an appropriate fit for the trial. Volunteers determine whether they are interested in participating (https://www.researchmatch.org).

Develop industry standards for working with biospecimens: ASCO will work with NCI and with colleagues in clinical research, pathology and epidemiology to develop more comprehensive standards and guidelines for biospecimen collection, storage and analysis. This work will build on successful molecular markers meetings and tutorials on biospecimens that have been sponsored by ASCO, NCI and the European Organization for Research and Treatment of Cancer.

Ensure that advances in HIT protect patients and researchers: ASCO will work with organizations in the oncology community and appropriate regulatory authorities (e.g., NCI, FDA and the HHS Office for Human Research Protections and Office for Civil Rights) to generate consensus on and support standards for patient privacy, information sharing and intellectual property protections to support HIT innovation.

CONCLUSION
The Way Forward

This report presents ASCO's vision for the future of translational and clinical research. ASCO's recommendations, when fully implemented, will help shorten the time between basic discoveries and development of new cancer therapies; focus efforts on therapies with the highest probability of success; and significantly improve the patient experience by enabling treatment to be better tailored to the needs of each individual.

We are not alone in our desire to revitalize clinical and translational research. Through our ongoing discussions with colleagues at research institutions, professional and patient organizations, federal agencies and industry, it is clear that others share many of the priorities laid out in this report — and all share our desire to accelerate the pace of research and offer patients more meaningful prevention, detection and treatment options.

This report lays out ASCO's initial recommendations and plans for implementation. We will build on these over the next decade, using this vision as a guidepost to map and evaluate our progress. As an organization representing cancer clinicians and researchers, ASCO plans to play a significant role in achieving the vision of this report. We are already working on several fronts to make this happen, and we hope to collaborate with many other stakeholders in the months and years ahead. Our major activities will include:

- **Building Consensus to Implement the Recommendations.** Over the next three years, ASCO plans to work with other stakeholders to convene working groups with experts from the scientific and regulatory communities, professional and patient advocate organizations and policymakers. The working groups will develop consensus recommendations on the topics identified in this report, including ways to develop biomarkers and surrogate endpoints, incentivize research collaboration, develop consensus on meaningful patient outcomes and research priorities, and increased use of innovative trial designs. ASCO will vet the consensus recommendations, seek peer-reviewed publication and work with advocacy partners to develop strategies for implementation.

- **Implementing ASCO Programs and Initiatives.** ASCO is engaged in and planning a number of activities to help improve clinical research. Several of these initiatives are noted in the Recommendations sections of this report. For example, ASCO is working to build a rapid learning system to improve cancer care and speed research. ASCO is also partnering with stakeholders to develop oncology-specific standards for HIT that are responsive to oncology practice, include quality measurement and improvement and integrate research. In addition, ASCO has conducted an analysis to determine how data sought in trials that study new uses for already-approved cancer treatments can be streamlined.[16] Future activities will include ongoing educational resources and support to help oncologists adapt to new research approaches.

- **Advocating for Policy Changes.** In many ways, revitalization of clinical and translational cancer research will depend on action by policymakers, including regulatory agencies. ASCO will continue working to raise awareness and build support for needed policy changes through consensus development, research and modeling of the impact of policy changes, new publications, events and other advocacy over the coming years.

GLOSSARY

Clinical Cancer Research
The branch of medical science that tests the safety and effectiveness of promising new drugs, devices and diagnostic products in humans. This research is often conducted through clinical trials that involve human participants and serve as the vital link between discoveries in the lab and new treatments that improve the lives of patients.

Biomarkers
Substances or biological features arising in tumor tissue, blood or other bodily fluids that can be identified through tests and used to diagnose or monitor cancer and its response to treatment.

Cancer Stem Cells
A class of cells that gives rise to other forms of cancer cells, and are thought to be the most critical to attack in order to stop cancer's spread and recurrence.

Cancerous Cells
Cells that are at any stage of becoming a cancer, from pre-cancer states to advanced cancer.

Genomics
The study of how specific genes, and genetic mutations, work together to influence the function of a cell. In oncology, researchers focus on identifying and targeting the genes, proteins and molecular pathways that enable cancer cells to develop, replicate, spread and resist certain therapies.

Health Information Technology
Health information technology (HIT) describes the management of health data that is shared securely – among health care providers, patients, researchers and insurers – through electronic health records and other technologies. Recent advances in HIT promise to help dramatically improve the quality of health care and allow researchers to more quickly identify and share promising treatment approaches.

Molecular Characterization
The process of analyzing cancer cells to evaluate the genes, proteins and biological pathways that drive cancer growth.

Nanotechnology
A field of technology utilizing materials on a scale 10,000 times smaller than a human cell to treat disease or accomplish other tasks, e.g., nanoparticles. Because of their very small size, these technologies offer potential new ways to deliver treatments directly to cancer cells.

Panomics
Panomics refers to the interaction of all biological functions within a cell and with other body functions, combining data collected by targeted tests (such as a HER2 test) and global assays (such as genome sequencing) with other patient-specific information. By synthesizing this information, researchers gain a deeper understanding of how multiple defects at the molecular level combine with factors in the tumor's environment to drive tumor development and behavior. This understanding is increasingly guiding drug development and targeted cancer therapeutic and prevention strategies.

Pathway

A series of interconnected genes and proteins that together control a certain function within a cell, such as cell division or death. Mutations anywhere along a pathway have the potential to disrupt normal cell function and result in cancer cell development and proliferation. Targeted drugs block specific cancer-related pathways, with the goal of causing cancer cell death while leaving healthy cells intact.

Patient-Reported Outcomes

Self-reported data from patients, most commonly related to symptoms, quality of life and other general health perceptions experienced during a medical treatment.

QOPI

ASCO's Quality Oncology Practice Initiative (QOPI®, see: http://qopi.asco.org/) is a physician-led, practice-based quality-improvement program used by oncology practices in the U.S. It measures practices' performance against evidence-based guidelines, and against other U.S. oncology practices, to give physicians detailed feedback and tools for improving the care they provide.

Rapid Learning System for Cancer Care

ASCO's proposed Rapid Learning System for Cancer Care will harness cutting-edge health information technology to connect cancer patients and their health care providers to a central knowledge base; synthesize information from millions of physician and patient experiences; and deliver up-to-the minute, personalized information to inform care for every patient. By collecting data in real time through electronic health records and other technologies, the system will also create a powerful new data source to generate new ideas for clinical research.

Surrogate Endpoint

As defined by the FDA, "A surrogate endpoint is a marker — a laboratory measurement, or physical sign — that is used in clinical trials as an indirect or substitute measurement that represents a clinically meaningful outcome, such as survival or symptom improvement. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval" (see: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/default.htm). For example, researchers may focus on tumor shrinkage or various biomarkers that indicate a treatment is having an effect. By identifying and validating surrogate endpoints for use in future trials, researchers have the potential to gain faster answers about the value of new therapies.

Translational Cancer Research

Translational research transforms scientific discoveries arising from laboratory, clinical or population studies into clinical applications to reduce cancer incidence, morbidity and mortality.

REFERENCES

1. National Cancer Institute. National Cancer Act of 1971. http://legislative.cancer.gov/history/phsa/1971

2. Kohler BA, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. *J Natl Cancer Inst*. 2011 May 4;103(9):714-36.

3. Howlader N, et al. SEER Cancer Statistics Review, 1975-2008, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, based on November 2010 SEER data submission, posted to the SEER web site, 2011

4. Stewart SL, et al. Cancer Mortality Surveillance—United States, 1990-2000. *MMWR Surveill Summ*. 2004 Jun 4;53(3):1-108.

5. Ferlay J, et al. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr

6. Institute of Medicine (IOM). 2010. *A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program*. Washington, DC: The National Academies Press.

7. Institute of Medicine. 2010. *Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary*. Washington, DC: The National Academies Press.

8. Wolff AC, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol*. 2007 Jan 1;25(1):118-45.l

9. Bast BC Jr. Status of tumor markers in ovarian cancer screening. *J Clin Oncol*. 2003 May 15;21(10 Suppl): 200s-205s

10. Weber WA. Positron emission tomography as an imaging biomarker. *J Clin Oncol*. 2006 Jul 10;24(20): 3282-92

11. Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet*. 2010 Aug 28;376(9742):687-697.

12. National Cancer Institute. Provocative Questions Page. http://provocativequestions.nci.nih.gov/

13. National Center for Research Resources. Clinical Research Networks. http://www.ncrr.nih.gov/clinical_research_resources/clinical_research_networks/index.asp

14. National Cancer Institute. Update on Implementation of Recommendations of the Guidelines Harmonization Working Group. http://deainfo.nci.nih.gov/advisory/ctac/1210/presentations/GHWG.pdf

15. National Cancer Institute. National Cancer Institute's Clinical Trials Cooperative Group Program. Available at http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group. Accessed October 19, 2011.

16. Kaiser LD, et al. Optimizing collection of adverse event data in cancer clinical trials supporting supplemental indications. *J Clin Oncol*. 2008 Dec 1;28(34):5046-53

17. National Cancer Institute. Transforming the National Cancer Institute Clinical Trials Enterprise. http://transformingtrials.cancer.gov/

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JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

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INTRODUCTION

Cancer clinical trials have typically investigated agents or regimens in patients selected for study based primarily on tumor histology and clinical characteristics. This approach, when successful, has too often resulted in only small incremental improvements in overall survival (OS) that likely reflect the impact of agents with modest efficacy in a subset of the study population that is not readily identifiable. Although this work has improved the lives of countless patients with cancer, it has been slow, costly, and empiric.

More recently, targeted therapies administered to patients selected by reliable and biologically relevant biomarkers have produced substantial improvements in outcomes that have rapidly transformed patient care for several cancer types.[1-5] As we improve our ability to identify the molecular drivers of cancer, it is reasonable to anticipate that highly effective, molecularly targeted regimens will continue to be introduced for use in patients who can be identified prospectively as likely to benefit from treatment.[6] In addition, newer treatment modalities such as immune therapy and antibody-drug conjugates are emerging as highly effective therapies that are providing improvements in patient outcomes far beyond what was achieved in the past.[7,8]

In this evolving paradigm, patients and physicians should expect that clinical trials will be designed to seek larger gains in selected groups of patients than have been achieved in the past. As articulated in the American Society of Clinical Oncology (ASCO) research blueprint,[9] these advances should allow us to implement clinical trials where meaningful advances in patient outcomes can be achieved with smaller numbers of trial participants (ie, smaller and smarter trials). On the basis of the rapid advances made in technology to interrogate the genome, we expect that the genomic tests used to guide cancer treatment will not only improve in sensitivity and specificity but also decrease the amount of biologic sample necessary and lower the cost and turnaround time to enable widespread use.

To examine these goals and opportunities, ASCO, via the ASCO Cancer Research Committee, convened four disease-specific working groups to consider the design of future clinical trials that would produce results that are clinically meaningful to patients (ie, significantly improved survival, quality of life [QOL], or both). Although the working groups did not restrict discussion to biomarker-driven clinical trials, the goals established will likely require enrichment strategies to achieve them. In the particular examples considered by the working groups, validated biomarkers are not currently available to select patients for treatment with specific drugs. However, we expect that over time, such biomarkers will be identified and that the goals set forth by these working groups will be achievable.

The conclusions reached by the working groups are not intended to set standards for regulatory approval or insurance coverage but rather to encourage patients and investigators to demand more from clinical trials. We recognize that the descriptions of clinically meaningful outcomes derived by the working groups are highly nuanced and influenced by clinical context, effectiveness and toxicity of available therapies, and patient goals and preferences and that they will likely change as the standard of care evolves in cancer treatment. Although OS was selected as the primary end point by all working groups, this does not diminish the value of progression-free survival (PFS) and other surrogate end points as valid end points in certain clinical situations. This is especially true in cancer types that often produce symptoms related to progressive disease, for example, painful bone metastases, where a significant prolongation in PFS may provide meaningful palliation and improved QOL.

The primary goal of the working groups was to help guide the development of definitive, randomized phase III trials, although each group recognized that it is imperative for investigators to obtain data

from well-conducted early-phase trials that will provide a strong foundation for the development of ambitious phase III studies. It is necessary to observe extremely strong signals in phase II studies if we are to expect clinically meaningful outcomes to be achieved in subsequent phase III studies. Although this statement may be obvious, we sometimes are more optimistic about results from phase II trials than is warranted.[10] It is even possible that phase III studies will not be necessary if results from well-conducted phase II trials demonstrate exceptional activity that clearly benefits patients.[11] A recent example is the development of crizotinib for treatment of *ALK*-translocated non–small-cell lung cancer, where phase II studies were sufficient to convince patients, oncologists, and the US Food and Drug Administration that accelerated approval was warranted because phase III studies were in progress.[12] Unfortunately, however, in many cases, targeted agents continue to be developed without a complete understanding of the drug target and therefore without development of a companion diagnostic to aid in patient selection. Thus, it is imperative that trial sponsors develop comprehensive biospecimen banks for each trial with informed consent from patients that will allow investigators to ask scientific questions before and after trials are completed to facilitate biomarker discovery and validation.[13]

WORKING GROUP DELIBERATIONS

The ASCO Cancer Research Committee convened four working groups composed of experts in carcinomas of the pancreas, breast, lung, and colon. An effort was undertaken to ensure broad stakeholder input and diverse points of view. Each working group included clinical investigators, patient advocates, biostatisticians, US Food and Drug Administration oncologists, and industry oncologists. Each working group met four to nine times over a 12-month period. Preliminary conclusions were posted for public comment on April 19, 2013, and more than 100 responses were obtained. This input was then considered by the working groups and integrated into the final conclusions presented here.

Each working group first selected a patient population as the focus of its deliberations and then selected primary and secondary end points for potential trials that would reflect clinically meaningful benefits to patients. Issues frequently discussed with respect to primary end point selection included the relationship of PFS to OS in a given clinical context. Although PFS is a commonly used end point, the working groups each preferred to use OS as the primary measure of clinically meaningful outcome. The groups acknowledged the challenges with OS, such as the need for longer follow-up and the potential confounding effect of poststudy therapies on assessment of the OS end point. The magnitude of the benefit that would be considered clinically meaningful engendered lengthy discussion, particularly in the breast cancer group, where consensus was not achieved. The groups discussed the need to balance the risks and benefits of therapy to define a clinically meaningful outcome in each clinical setting.

The working groups acknowledged that crossover in clinical trials is increasingly common, because it offers patients a greater chance to receive the experimental treatment than fixed-arm trials. Clearly, trials can be designed that demonstrate clinically meaningful outcomes without affecting OS, such as trials that demonstrate noninferiority compared with existing therapies with significantly less toxicity. In addition, we are now able to identify secondary mutations that drive tumor growth after progression during first-line targeted therapies.[14] Although this information provides an opportunity for success in second-line therapies, it also makes OS a more difficult end point to attain. Thus, the use of PFS as a clinically meaningful end point may be appropriate in particular disease settings and has, in fact, been accepted by regulatory authorities on many occasions already.[15-17]

A common theme that arose in all working group discussions was the issue of QOL, and all agreed that QOL is difficult to measure and interpret, even when using validated instruments. In particular, the challenge in defining a clinically meaningful change score in global QOL measures was noted. In more recent years, interest has therefore shifted to focus on a patient's specific symptom burden and engaging the patient in reporting directly on his or her symptoms. The working groups expressed the view that serial assessment of specific cancer-related symptoms, using validated instruments and shorter, more cancer-specific surveys, can define a clinically meaningful outcome for patients, as evidenced by the 2011 approval of ruxolitinib for treatment of myelofibrosis.[18]

Patient symptoms resulting from cancer progression and tolerability of treatment-related toxicities are of critical importance when considering whether a new treatment produces a clinically meaningful outcome for patients. For the most part, the working groups agreed that if a therapy is less toxic than prevailing treatments, a smaller improvement in efficacy is acceptable. Conversely, a highly toxic therapy should be accompanied by an expectation of substantially greater benefit to provide a clinically meaningful outcome to patients.

To address the nuances of balancing toxicity with efficacy as well as QOL outcomes, working groups used ranges of time and hazard ratios (HRs) to describe clinically meaningful outcomes in each disease setting. However, it was generally agreed that relative improvements in median OS of at least 20% are necessary to define a clinically meaningful improvement in outcome.

OUTCOME OF THE WORKING GROUP DISCUSSIONS

The conclusions of the working groups are summarized in Table 1. All but the colon cancer group focused on patients with metastatic disease receiving first-line systemic treatment, and all groups selected OS as the primary clinical end point of interest. Each group identified an HR ≤ 0.8 corresponding to an improvement in median OS within a range of 2.5 to 6 months, depending on the clinical context, as the minimum incremental improvement over standard therapy that would define a clinically meaningful outcome. Secondary efficacy end points of interest are summarized in Table 1 as well. Each working group felt that the incremental gains shown in Table 1 should be accompanied by little to no increase in toxicity compared with prevailing therapies and that new regimens that are substantially more toxic than current standards should also produce the greatest increments in OS to be considered as having achieved a clinically meaningful outcome. Statisticians in each group provided information regarding the number of patients necessary for study based on the ranges for OS improvement (and HRs) provided by each working group (Appendix, online only).

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)	Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

DISCUSSION

This project undertaken by four groups of experts to define clinically meaningful outcomes for cancer clinical trials provides an example of the deliberations that we believe clinical trial sponsors and investigators should undertake in developing new therapies for patients with advanced cancer. We are calling on the community of patients, patient advocates, and clinical investigators to collectively raise the bar in our expectations of the benefits of new therapies. The benchmarks we propose highlight the promise of predictive biomarkers and their associated targeted therapeutics to achieve these goals. We recognize that at present, no validated biomarkers exist to guide patient selection for clinical trials in any of the clinical scenarios described here. Thus, the outcomes discussed here can only be considered aspirational at this time. The goals put forth are the result of extensive discussion and compromise among working group members, input from the public, and insight from ASCO committees and leaders. Consensus was hard to come by, as expected. Nearly all of the working groups and stakeholders agreed that we are now in a new era, where molecular tools can be used to identify specific patient subpopulations likely to benefit from targeted therapies that in turn will lead to substantially improved treatment outcomes. Unfortunately, even with these tools already in hand for some cancers, incremental gains are still small, measured in weeks, not months or years, and often transient. Thus, much work remains to be done to optimize treatment regimens and suppress or circumvent drug resistance. Even so, the recent development of crizotinib and vemurafenib,[2-4,7] each with a companion diagnostic, provides tangible evidence that the approaches and goals laid out here are achievable and encourages us to seek even more effective therapies for common cancers.

A focus on defining meaningful outcomes for patients will also contribute important information and perspective to ongoing discussions in many venues about improving the value of health care in general and cancer care in particular. Value can be defined in various ways, although a patient-centric definition considers patient outcomes in the context of the cost of delivering those outcomes.[27] Because clinical trial results provide the gold standard for defining treatment efficacy, the deliberations of the working groups around the concept of clinically meaningful outcomes will help inform discussions about optimizing value in cancer care. Indeed, the ASCO Value of Cancer Care Task Force has been formed to consider how efficacy, toxicity, and cost can be weighted to best describe the value of specific treatment interventions.

We hope that the exercise described here will inspire investigators to raise the bar in an effort to significantly advance cancer care. We encourage physicians who are considering implementing trials to select those trials that are designed to deliver the most benefit to patients. We anticipate that patient advocates who are participating in peer-review programs, institutional review boards, and protocol design committees will also begin to demand more from trials. We hope that clinical trial sponsors will have a better understanding of patients' and investigators' expectations when weighing research and funding priorities for their pipeline molecules. Trials that are designed with less ambitious goals than described here may still be of benefit to individual patients if trial end points are met. However, we believe that investigators and sponsors who accept the challenges laid out here are more likely to make true advances in drug and device development that will change paradigms in cancer care and, in so doing, provide clinically meaningful outcomes for our patients. As always, discussing the value of clinical trials with patients and explaining the goals of such trials are essential in the comprehensive care of those with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al: Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. N Engl J Med 366:2180-2188, 2012

2. Von Hoff DD, LoRusso PM, Rudin CM, et al: Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. N Engl J Med 361:1164-1172, 2009

3. Kwak EL, Bang YJ, Camidge DR, et al: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 363:1693-1703, 2010

4. Chapman PB, Hauschild A, Robert C, et al: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364: 2507-2516, 2011

5. Flaherty KT, Puzanov I, Kim KB, et al: Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med 363:809-819, 2010

6. Vogelstein B, Papadopoulos N, Velculescu VE, et al: Cancer genome landscapes. Science 339: 1546-1558, 2013

7. Hodi FS, O'Day SJ, McDermott DF, et al: Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363:711-723, 2010

8. Verma S, Miles D, Gianni L, et al: Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367:1783-1791, 2012

9. Meropol NJ, Kris MG, Winer EP: The American Society of Clinical Oncology's blueprint for transforming clinical and translational cancer research. J Clin Oncol 30:690-691, 2012

10. Maitland ML, Hudoba C, Snider KL, et al: Analysis of the yield of phase II combination therapy trials in medical oncology. Clin Cancer Res 16:5296-5302, 2010

11. Sharma MR, Schilsky RL: Role of randomized phase III trials in an era of effective targeted therapies. Nat Rev Clin Oncol 9:208-214, 2011

12. National Cancer Institute: FDA approval for crizotinib. http://www.cancer.gov/cancertopics/druginfo/fda-crizotinib

13. Hayes DF, Allen J, Compton C, et al: Breaking a vicious cycle. Sci Transl Med 5:196cm6, 2013

14. Diaz LA Jr, Williams RT, Wu J, et al: The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. Nature 486:537-540, 2012

15. Blumenthal GM, Scher NS, Cortazar P, et al: First FDA approval of dual anti-HER2 regimen: Pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer. Clin Cancer Res 19:4911-4916, 2013

16. Casak SJ, Lemery SJ, Shen YL, et al: U.S. Food and Drug Administration approval: Rituximab in combination with fludarabine and cyclophosphamide for the treatment of patients with chronic lymphocytic leukemia. Oncologist 16:97-104, 2011

17. Thornton K, Kim G, Maher VE, et al: Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. Clin Cancer Res 18:3722-3730, 2012

18. Deisseroth A, Kaminskas E, Grillo J, et al: U.S. Food and Drug Administration approval: Ruxolitinib for the treatment of patients with intermediate and high-risk myelofibrosis. Clin Cancer Res 18:3212-3217, 2012

19. Conroy T, Desseigne F, Ychou M, et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817-1825, 2011

20. Kindler HL, Ioka T, Richel DJ, et al: Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: A double-blind randomised phase 3 study. Lancet Oncol 12:256-262, 2011

21. Von Hoff DD, Ervin T, Arena FP, et al: Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369: 1691-1703, 2013

22. Pirker R, Pereira JR, von Pawel J, et al: EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: Analysis of data from the phase 3 FLEX study. Lancet Oncol 13:33-42, 2012

23. Rossi A, Di Maio M, Chiodini P, et al: Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: The COCIS meta-analysis of individual patient data. J Clin Oncol 30:1692-1698, 2012

24. O'Shaughnessy JA, Kaufmann M, Siedentopf F, et al: Capecitabine monotherapy: Review of studies in first-line HER-2-negative metastatic breast cancer. Oncologist 17:476-484, 2012

25. Cortazar P, Justice R, Johnson J, et al: US Food and Drug Administration approval overview in metastatic breast cancer. J Clin Oncol 30:1705-1711, 2012

26. Grothey A, Van Cutsem E, Sobrero A, et al: Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:303-312, 2013

27. Porter ME: What is value in health care? N Engl J Med 363:2477-2481, 2010

Appendix

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General Overview of Design Considerations for All Disease Types

The following assumptions are true of all designs considered:

- Two-arm trial with 1:1 randomization
- Two-sided α level of 0.05
- No interim analyses were included in the sample size projections
- Power of 80% or 90% to detect target hazard ratio on overall survival (OS) end point

Although interim analyses are not part of these calculations, it is widely supported that interim analyses for futility and efficacy should be considered when planning randomized phase III trials. Including one or more interim analyses would modestly affect these required sample sizes ($<$ 5% impact on total sample size). It is also often appropriate to perform one-sided testing or opt for unbalanced randomization. Switching to one-sided testing would reduce the required sample size by approximately 20%. Switching to a 2:1 randomization would require an increase in sample size of approximately 15%. Because of differences in patient populations and median OS, individual disease working groups have chosen different expected times of accrual and follow-up times.

Design Considerations for Metastatic Pancreatic Cancer Phase III Trial

Assumptions:

- Accrual of 18 months
- Minimum 12-month follow-up for all patients

Scenarios considered (Appendix Table A1, online only):

- Median survival in control group, 6 months (gemcitabine population); goal: increase median survival 10 to months (hazard ratio [HR] of 0.60, assuming exponential survival function)
- Median survival in control group, 10 months (FOLFIRINOX [leucovorin, fluorouracil, irinotecan, and oxaliplatin] –eligible population); goal: increase median survival 15 to months (HR of 0.67, assuming exponential survival function)

Design Considerations for Metastatic/Stage IV Lung Cancer Phase III Trial

Assumptions:

- Accrual of 18 months
- Minimum 18-month follow-up for all patients

Scenarios considered (Appendix Table A2, online only):

- For patients with nonsquamous cell carcinoma: median survival in control group, 13 months; goal: increase median survival to 17 months (HR of 1.3, assuming exponential survival function)
- For patients with squamous cell carcinoma: median survival in control group, 10 months; goal: increase median survival to 13 months (HR of 1.3, assuming exponential survival function)

Design Considerations for Metastatic Triple-Negative Breast Cancer Phase III Trial

Assumptions:

- Accrual of 24 months
- Minimum 36-month follow-up for all patients

Scenario considered (Appendix Table A3, online only):

- Two-arm study designs for selected median survivals and improvements in median survivals for patients with metastatic triple-negative breast cancer

Design Considerations for Metastatic Colorectal Cancer Phase III Trial

Assumptions:

- Accrual of 12 months
- Minimum 12-month follow-up for all patients

Scenarios considered (Appendix Table A4, online only):

- Median survival in control group, 4 months; goal: increase median survival by 5 to 9 months (HR of 0.44, assuming exponential survival function)
- Median survival in control group, 4 months; goal: increase median survival by 3 to 7 months (HR, 0.57); also approximately applicable to increasing median survival from 6 to 11 months (HR, 0.55)
- Median survival in control group, 6 months; goal: increase median survival by 3 to 9 months (HR, 0.67); also corresponds to increasing 1-year survival from 25% to 40%
- One-year survival in control group, 25%; goal: increase 1-year survival by 10% to 35% (HR, 0.76)

Table A1. Metastatic Pancreatic Cancer Phase III Trial

Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	No. of Events Required (total)	Sample Size Required per Arm
6	10	0.60	0.80	120	73
			0.90	160	97
8.5	12.5	0.68	0.80	211	143
			0.90	284	192
10	15	0.67	0.80	191	140
			0.90	256	188

Abbreviation: HR, hazard ratio.

Table A2. Metastatic/Stage IV Lung Cancer Phase III Trial

Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	No. of Events Required (total)	Sample Size Required per Arm
13	17	0.76	0.80	438	306 (612 total)
			0.90	587	414 (828 total)
10	13	0.77	0.80	457	288 (576 total)
			0.90	612	387 (774 total)

Abbreviation: HR, hazard ratio.

Table A3. Metastatic Triple-Negative Breast Cancer Phase III Trial

Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	No. of Events Required (total)	Sample Size Required
12	18	0.67	0.80	196	220
			0.90	262	290
15	21	0.71	0.80	268	330
			0.90	358	440
18	24	0.75	0.80	380	480
			0.90	508	640
21	27	0.78	0.80	509	660
			0.90	681	880
12	16	0.75	0.80	380	420
			0.90	505	560
15	19	0.79	0.80	566	660
			0.90	756	870
18	22	0.82	0.80	789	960
			0.90	1,067	1,280
21	25	0.84	0.80	1,033	1,360
			0.90	1,382	1,790

Abbreviation: HR, hazard ratio.

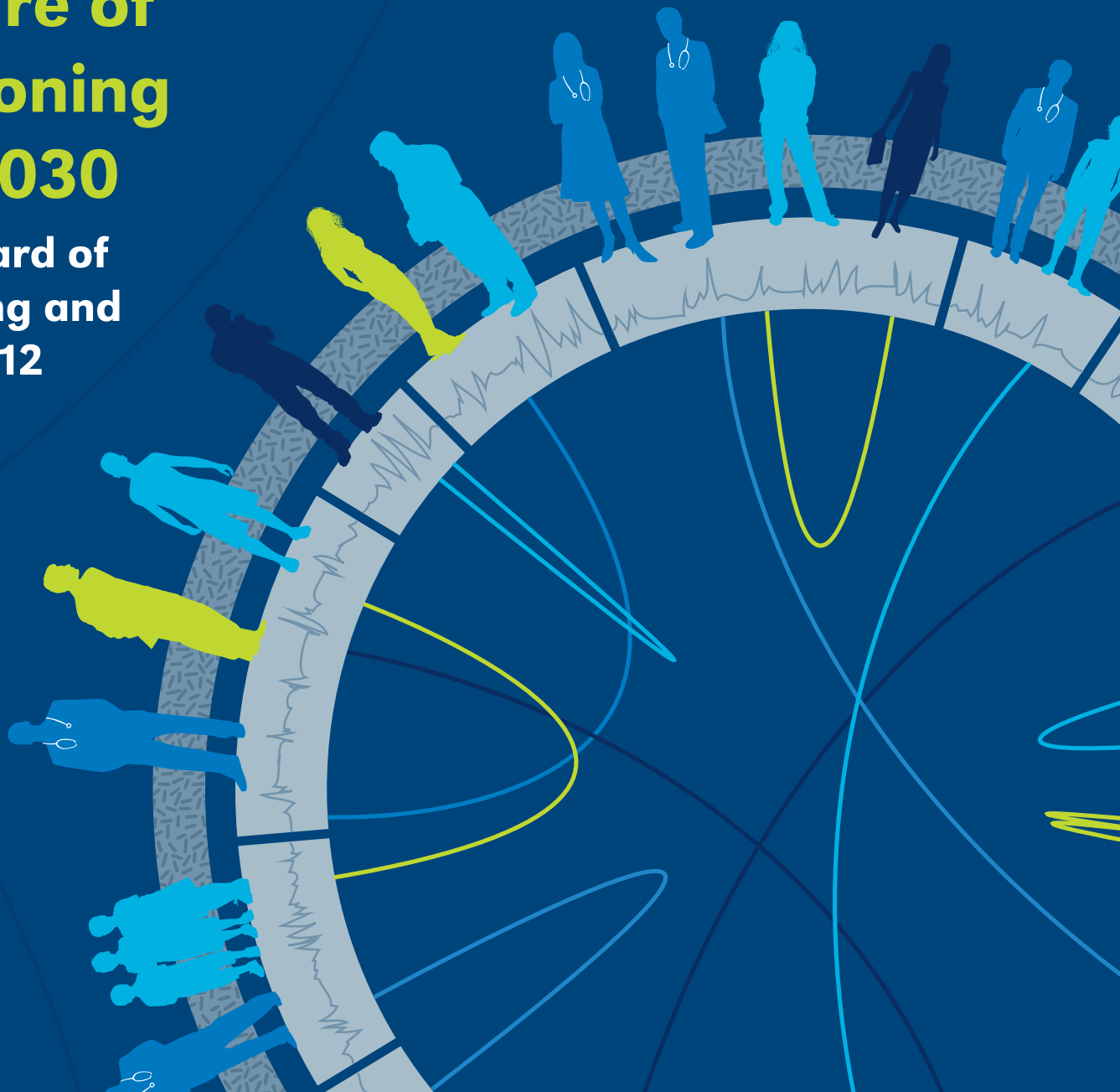
Table A4. Metastatic Colorectal Cancer Phase III Trial

Scenario	Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	Sample Size Required per Arm
1	4	9	0.44	0.80	30
				0.90	40
2	4	7	0.57	0.80	60
				0.90	80
3	6	9	0.67	0.80	120
				0.90	160
4	1-year OS, 25%	1-year OS, 35%	0.76	0.80	250
				0.90	340

Abbreviations: HR, hazard ratio; OS, overall survival.

Shaping the Future of Oncology: Envisioning Cancer Care in 2030

Outcomes of the ASCO Board of Directors Strategic Planning and Visioning Process, 2011-2012



ASCO®
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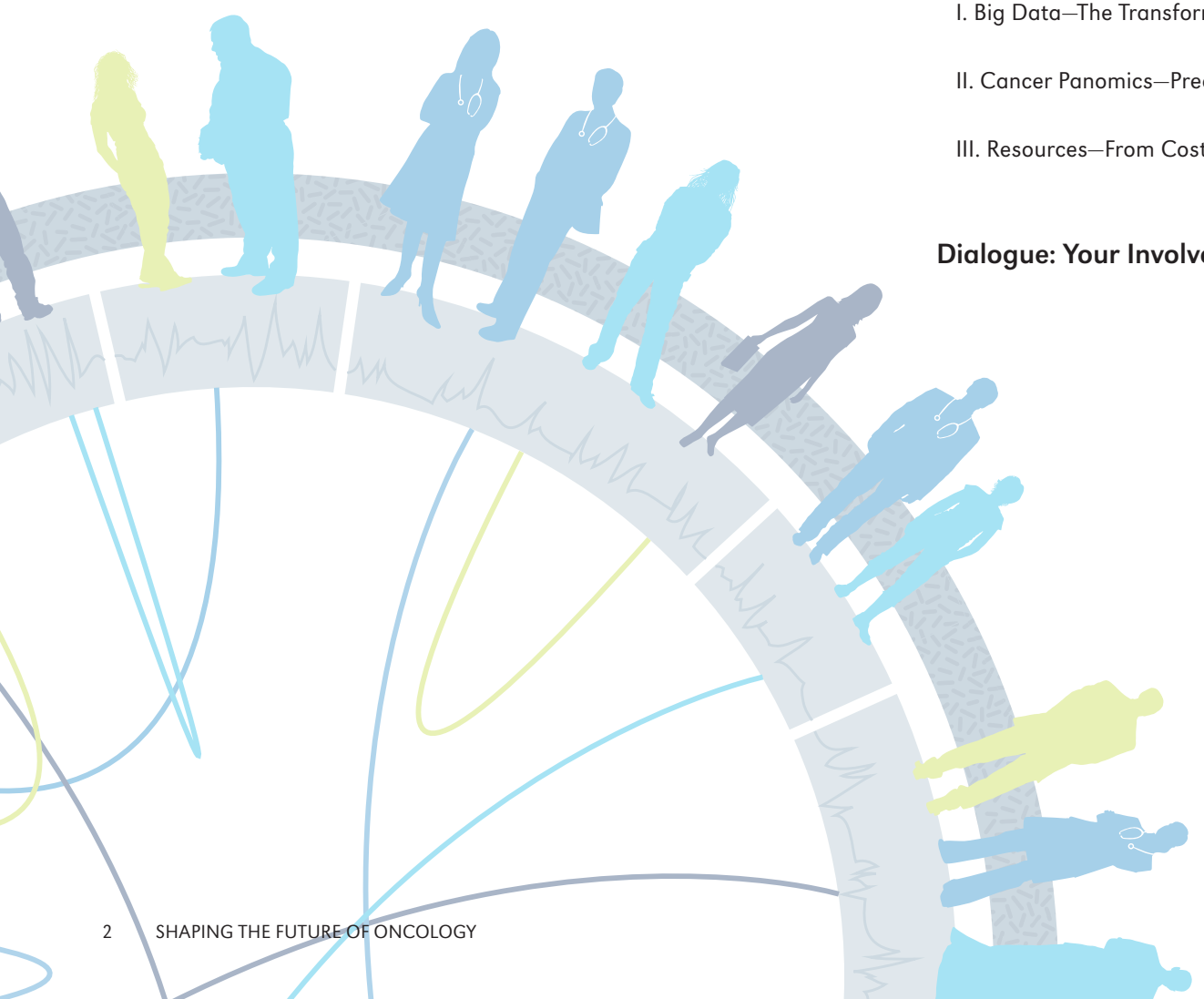


FOREWORD: Charting the Future Together

Over fifty years of modern oncology, our profession has delivered scientific advances and improved outcomes for patients, significantly increasing cancer survival and quality of life.

However, the forces that fueled this progress are not the same as those that will shape the future. Oncology leaders, scientists and clinicians agree: we are on the verge of a new age of cancer care, in which emerging scientific, technical and economic trends are likely to alter our work more significantly in the next 20 years than in the prior 50. As a profession, we must anticipate and harness these changes if we are to improve the care of our patients.

By anticipating the future, we can shape it. Over a six-month period, ASCO's Board of Directors worked to identify and understand the major "drivers of change" and the potential consequences of these changes for our field over the next two decades. Through interviews with thought leaders and a series of strategic planning exercises (see sidebar), we have begun to formulate a vision of oncology in 2030.

The Board identified three key drivers of change that will have the biggest impact on cancer care over the coming decades:

- **"Big data".** Rapid advances in health information technology (HIT) have created unprecedented opportunities to collect, analyze and learn from vast amounts of real-world data
- **Cancer panomics.** We are coming to understand the complex networks of molecular pathways and characteristics of the tumor microenvironment that interact to drive cancer and will need to be targeted, in combination, to develop prevention strategies and curative therapies
- **Delivering value.** Unsustainable cost increases and improvements in quality metrics are leading to a growing focus on cost effectiveness and "value" in health care

This document reflects the outcomes of the Board's discussions. It presents one possible vision of the future—by no means the only one—and identifies the major obstacles to achieving that vision. It is intended to spark a dynamic, ongoing discussion with you, ASCO's members, about where our field is headed and where we want to be in 20 years. And it will help ASCO determine future needs and solutions for the profession that will help us serve you, and help you serve your patients.

ASCO's Visioning Process

ASCO's Board of Directors began the work of developing this vision in September 2011. Board members worked with ASCO staff to obtain input from an array of ASCO volunteers and external thought leaders. Key steps in the process included:

- A virtual town hall meeting with physician volunteers from ASCO's committees
- In-depth interviews with more than 20 external thought leaders, representing diverse backgrounds and fields ranging from clinical research to information technology
- Identification of three major drivers of change based on volunteer and thought leader input
- Identification of likely consequences of each driver, through a facilitated Board discussion in March 2012

This document reflects the outcomes of these discussions. It was developed by ASCO staff and reviewed and approved by the Board in September 2012.

VISION: Cancer Care in 2030

I. Big Data—The Transformation of Cancer Care through Health Information Technology

Rapid progress is being made in the development and implementation of HIT. From improved data storage and processing speeds to new ways of analyzing "unstructured" notes in electronic health records (EHRs), HIT holds the promise to help transform how we care for our patients over the next two decades.

"The more we work with big data, the more noise we can filter out—even when some of the data is wrong. Accuracy is very important with tiny data streams, but not so much with large data streams."

—**John Seely Brown,** *visiting scholar and advisor to the Provost, University of Southern California; Independent Co-Chairman, Deloitte Center for the Edge*

Vision for 2030

Learning from every patient. Today, very little is known in the aggregate about the care of most patients with cancer, let alone the efficacy outcomes and toxicity they experience. But in the coming years, HIT advances will enable us to draw insight from vast quantities of "real-world" data that currently are locked away in unconnected servers and file cabinets.

By 2030, we envision that the oncology field will be able to:

- **Analyze and share data on every patient with cancer.** Oncology practices will participate in IT-based systems that interact with EHRs to securely compile and analyze information on patient characteristics (e.g., molecular profiles, comorbidities), treatments, clinical outcomes and long-term side effects and other survivorship issues. ASCO's CancerLinQ™ initiative, currently in the planning stages, will have been fully implemented and adopted to serve this role.
- **Draw immediate practice-changing conclusions from an immense body of observational data.** By aggregating and analyzing data from millions of patient experiences in real time, CancerLinQ or similar systems will identify trends and associations between myriad variables and generate new hypotheses. Physicians and researchers will evaluate those hypotheses and determine which ones lead to improved care in real-world settings. This routinely will enable clinicians and researchers to apply those conclusions quickly to the care of their patients.
- **Transform clinical guidelines into living, "crowd-sourced" documents.** Instead of relying solely on clinical trials and expert analyses, guidelines will be informed by robust conclusions drawn from real-world care. Through CancerLinQ or other IT-based systems, guidelines, once developed, will be tested continually and refined as the

"We are moving toward a data-driven approach to cancer research and treatment, and away from a model that is only guideline driven. We will be looking for smaller and smaller sub-populations, so it will be critical to engage all providers and collect data across all institutions and practices."

—**Dr. Mia Levy,** *Director, Cancer Clinical Informatics, Vanderbilt Ingram Cancer Center*

Putting Observational Data to Work

While clinical trials will likely remain the gold standard of evidence for cancer therapy, HIT advances promise to help transcend the current limitations of observational data and provide powerful new ways to advance patient care.

The explanatory power of today's observational databases is severely limited. Most of these, including typical EHR databases, are too small to draw valid conclusions. When larger databases do exist—for example, payer databases or adverse event reporting systems—their narrow scope makes it impossible to answer questions other than those they were designed to address.

A rapid learning system such as ASCO's CancerLinQ will help overcome these challenges. In essence, CancerLinQ will be designed to accept all available information about the characteristics, care and outcomes of real-world patients. With this massive body of unstructured data, together with the use of advanced HIT tools, it will be possible to:

- "Normalize" similar information even if provided in different formats, overcoming the wide variation in EHR data standards
- Run the data through "correlation engines" and trend analysis tools, revealing connections that had never been visible before
- Draw statistically valid conclusions that extend the findings of clinical research (e.g., in new patient populations or settings)
- Develop robust hypotheses that could be confirmed through streamlined clinical research
- Provide clinical decision support based on observational analysis

resulting outcomes are analyzed in real time. This process will dramatically reduce the time required to synthesize new knowledge: guidelines will become more detailed, more accurate and completed in far less time than it takes today.

The oncologist's role, transformed. By 2030, health care professionals will receive robust and truly informative decision support at the point of care through CancerLinQ or similar systems—a necessity in an age of highly personalized care.

As a result of this real-time guidance, most oncology care will, in effect, be rule-based. The shift to rule-based care will have significant implications for the oncology workforce:

- **Other providers will play a large role in routine oncology care.** For less complex cancer cases and in follow-up care for a growing number of cancer survivors, primary care physicians, physician assistants or nurse practitioners will be equipped to provide care based on CancerLinQ and consultation with oncologists. Oncologists, in turn, will make better use of their deep expertise. They will focus on developing treatment plans, managing care teams, collaborating with primary care providers, and overseeing complex cases where the "rules" remain unclear.
- **The increased involvement of non-specialists will mitigate, though not eliminate, the oncologist shortage that is projected as the population ages and cancer incidence increases.** As oncologists are freed up from activities that do not capitalize on their unique expertise, they will be able to guide or oversee care for larger numbers of patients. However, shortages of primary care professionals will also need to be addressed in order to make this possible and to address the needs of cancer survivors.

"We need to figure out what exactly it means for oncologists to only do what is needed by an oncologist—and allied health workers should do the rest."

—**Dr. Mark McClellan,** *Director, Engelberg Center for Healthcare Reform, Brookings Institute*

Patients as full partners. Through personalized, patient-friendly HIT tools, patients will have a much greater opportunity to serve as well-informed advocates for their own care. While not every patient will take advantage of these possibilities, most will. By 2030, the results will include:

- **A significant shift in the doctor-patient relationship.** By the time patients arrive for consultation with an oncologist, most will already know a great deal about their cancer, thanks to personalized information from patient portals in CancerLinQ or other systems. They will expect to contribute to all important decisions about their care, while looking to their physician to suggest alternatives. Although oncologists will give up a measure of "control" in the relationship, they will have much greater confidence that treatment plans truly reflect their patients' wishes.
- **Through patient-friendly HIT interfaces, patients will stay connected with their oncologists and other providers in real time.** Whenever treatment plans or clinical information are updated in patients' medical records, they will be able to see and understand the implications. They will take an active role in their care by reporting their health status, side effects and other experiences as they happen—and will rest easier knowing their oncology team is monitoring for anything that warrants special attention.
- **The majority of patients will participate in clinical research, and we will learn valuable information from every patient we encounter.** HIT-driven interfaces will help match patients with appropriate studies from the moment they are diagnosed, based on the molecular profile of their tumors and other characteristics. Patients will have greater understanding and appreciation of clinical research and will come to see it as a part of routine cancer care, in part because enrollment procedures will become simpler and more patient- and provider-friendly.
- **New disparities may arise from the shift in patient involvement.** Since not all patients are equally motivated or equipped to drive their own care, disparities may emerge as patients are expected to play a greater role. The oncology community will have to find ways to continue meeting the needs of individuals who want, or need, to rely more heavily on their physicians to guide their care.

State-of-the-art oncology goes global. Global HIT systems will allow physicians and patients anywhere in the world to benefit from the latest, best available knowledge, helping to reduce today's glaring global disparities in cancer care.

- **Low-resource countries will contribute to, and benefit from, global rapid**

learning networks. The benefits of robust clinical decision support will be greatest in nations where oncologists are in short supply, and where other health providers must provide the lion's share of cancer care. At the same time, the experiences of patients in these countries will lead to the development of meaningful international clinical guidelines.

- **Cancer research will be a truly global enterprise,** as HIT systems link researchers, patients and research procedures, even in the most remote locations, and as molecular testing—a central element of nearly all clinical cancer research—becomes affordable and ubiquitous.

"The movement from the classic model of physician decision-making to shared decision-making is going to make a big impact on healthcare. Oncology could be in a great position to lead the movement."

—**Dr. John Wennberg,** *Professor, The Dartmouth Institute*

Obstacles to Overcome

While we believe the vision above to be realistic, the oncology community will need to overcome several significant obstacles in order to get there. These include:

- **Uncertainty or inconsistency in IT development and adoption.** The vision above assumes that information technologies—from processing power and storage capacity to new data standards and analysis—will continue their rapid advancement and will be effectively adopted as they become available. While IT advances historically have surpassed expectations, there are no guarantees that this will continue. At the same time, the oncology community will need to push the envelope in adopting new IT approaches—something we have not always done well, as in the case of EHRs. We will also need to work together to ensure the interoperability of various systems, a condition that has often not been met with EHRs to date.
- **Looming primary care physician shortages.** Like oncology, the primary care field faces a severe physician shortage in the coming years, reinforcing the need for greater involvement of nurse practitioners and physician assistants in cancer care. Primary care providers will also require significant oncology training, provided by ASCO and other institutions, to take on an increased role.
- **Globally, wide variation in resources and professional capacity and infrastructure.** While HIT advances promise to help patients in any part of the world, their impact won't be uniform. Countries with the fewest healthcare resources today will be the least equipped to make use of new technologies tomorrow. To avoid further disparities, global health programs may need to include a major focus on improving IT capacity and training in low-resource countries.
- **Limits of patient involvement and expertise.** Our vision may test the limits of what patients are willing or able to take on. Oncologists and patient advocates will need to devote significant time and resources to developing patient-friendly ways of presenting real-time information. Oncologists will also need to remain aggressive advocates for our patients—especially those less able to advocate for themselves.

II. Cancer Panomics—Precision Medicine Realized

While targeted and individualized treatments already have begun to transform cancer care, our growing understanding of the biology of cancer will take targeted therapy to an entirely new level in the coming decades. Instead of targeting individual pathways in cancer cells, we will have the tools to address the panomics of cancer—the complex combination of patient-specific characteristics that drive the development of each person's disease, response to therapy and long-term toxicities.

"Going forward it will not be acceptable to be satisfied with 20-30% response rates and celebrate the impact. Successes will be more like crizotinib and ALK1—a response rate that our infectious disease colleagues would be proud of. That is where it is going. The question is when."

—**Dr. Harish Dave,** *Global Therapeutic Head of Hematology and Oncology, Quintiles*

Vision for 2030

Smarter care, better care. Panomics will be the driving force behind the vast majority of cancer care, enabling providers to individualize treatment for each patient. Specifically, by 2030:

- **Panomic tools will be simple, affordable, and ubiquitous.** This will allow not only oncologists, but often primary care teams, to diagnose and characterize the factors driving a given patient's cancer—the key step in obtaining decision support to guide therapy.
- **A significant share of all cancers will be molecularly well-understood and highly treatable.** While the work of characterizing all cancers will take decades, by 2030 many of the most common cancers—accounting for the majority of patients—will be well understood and effectively targeted.
- **Combination targeted therapy will be the standard of care for most cancers.** Oncologists will understand which panomic "hubs" must be targeted in the complex network of molecular pathways that drive common cancers. By targeting these molecular defects in combination, treatment will lead to better disease control and prevent recurrences for many more patients.
- **Cancer prevention and detection will come of age.** Validated biomarkers will help identify many patients at risk of developing cancer, enabling providers to preempt the cancer's development through early treatment or prevention strategies. Most of this work will occur in primary care settings, due to greater collaboration between oncologists and other providers, along with ubiquitous access to molecular testing.

Biospecimens as a common good. The future of molecularly based cancer care will be built upon access to vast quantities of annotated biospecimens. Aided by the IT advances above, virtually all institutions will participate in systems to collect and share data on biospecimens, increasing the pace of discovery and reinforcing the view that every patient with cancer can contribute to progress.

- **Biospecimen collection and analysis will become standard practice, enabled by quick and affordable technologies and efforts to forge agreement on suitable assays.** The ability to analyze blood or circulating tumor cells, together with advances in interventional radiology, will enable many patients to contribute useful biospecimens without invasive surgical biopsies and procedures.
- **Public dialogue will establish biospecimen contribution as a collective responsibility.** Greater awareness of the benefits of biospecimen collection—by patients, policymakers and the public—will lead to greater

"For our early-phase trials I had to boil it down to something really simple: No tissue. No marker. No study."

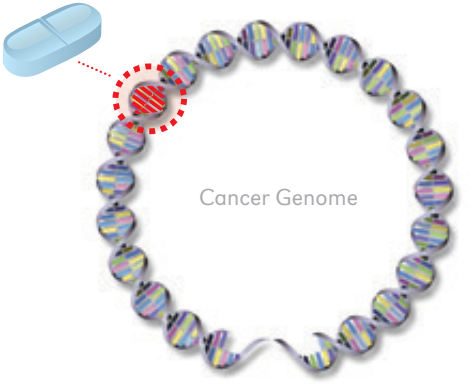
—**Dr. James Doroshow,** *Deputy Director, Clinical & Translational Research, National Cancer Institute*

willingness to contribute genetic and clinical information as a routine part of care. This shift in attitude will be made possible as data security and privacy concerns are effectively addressed though HIT advances and the streamlining of informed consent to one-time consent for all future use of biospecimens.

Clinical cancer research for the panomic era. As cancer becomes more narrowly defined by patient-specific characteristics, traditional approaches to clinical research will quickly become scientifically and financially untenable. Treatments will essentially consist of many different "orphan drugs" that must be tested in varying combinations among small, molecularly defined patient populations. To adapt to this reality by 2030:

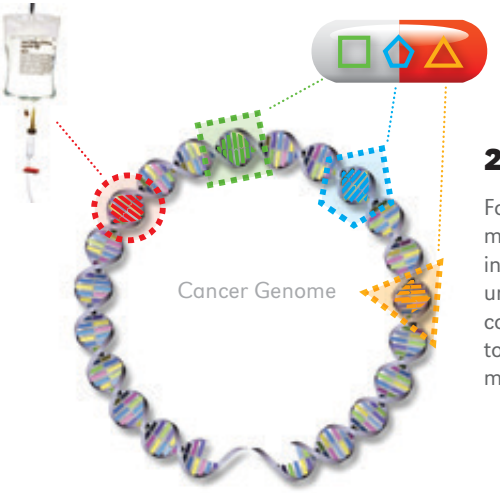
- **Research sponsors and the U.S. Food and Drug Administration (FDA) will agree on streamlined trial designs.** To ensure that trials can be smaller, faster and cheaper, these stakeholders will need to develop new trial designs and endpoints that can lead to rapid approval. Survival, while still an ideal endpoint, will be replaced in many trials by validated biomarker-based endpoints that correspond to meaningful clinical improvements for patients. ASCO will have played a key role in brokering this change, building on the vision laid out its 2011 *Blueprint for Transforming Clinical and Translational Cancer Research.*
- **Clinical research will be aided by powerful observational research.** CancerLinQ or other rapid learning systems will enable researchers to corroborate the findings of smaller, faster clinical trials as drugs are put to use in real-world settings. FDA will accept, and may even require, such post-marketing observational research in order to solidify its provisional approvals, and to provide real-time safety monitoring of new therapies in the field.
- **Companies will routinely collaborate on drug development.** As drugs are increasingly tested in combination, companies will find this to be the only viable

Targeted Cancer Therapy—Today and 2030



Today

Available drugs target single mutations within the cancer genome, often resulting in only temporary delays in progression and limited impact on survival.



2030

For common cancers, multiple targets and their interactions will be understood. Treatment combinations will be tailored to the individual patient's molecular profile.

way to continue developing cancer therapies, as well as a powerful way to create efficiencies in testing many different drugs in narrowly defined populations, making research more cost effective.

Obstacles to Overcome

Significant challenges to achieving this vision will include:

- **Threats to drug development.** Revamping clinical research approaches will be a difficult process involving many different stakeholders—physicians, researchers, industry, federal agencies, advocates, health insurers and others. In many cases, these groups will have competing priorities and perspectives. There is an urgent need to find common ground in time to avoid major disruptions in cancer drug development.
- **Unprecedented data storage and management needs.** As data from millions of patient biospecimens are collected, the analysis and storage requirements will dwarf those of all prior genome sequencing efforts. Along with the basic technological challenge of storing data on servers or "in the cloud", the oncology community will need to reach consensus on who should annotate, store and interpret this information, and how it will be made available to those who need it. New collaborations with mathematicians, computer engineers and physicists will also be required in order to analyze the complex molecular pathways identified through biospecimen analysis.
- **Biospecimen privacy, security and informed consent.** At a fundamental level, we will need to determine how to maintain patient privacy when an individual's genome is more specific than any other personal information. Will de-identification be possible? In practical terms, we must be able to educate and reassure a public that remains skeptical of medical data-sharing.
- **Limited laboratory infrastructure.** Routine panomic analysis will require laboratory capacity and expertise on a scale that does not yet exist. Building this infrastructure will require significant financial investments, and also hinges on important decisions about where these facilities will be housed and how centralized they should be.

"The placebo controlled trial has been the hallmark of clinical development for decades despite significant scientific advances. The FDA system needs to reform to keep pace with innovation. Otherwise, R&D will become too costly to pursue for many partners."

—**Christopher A. Viehbacher,** *CEO, Sanofi*

Streamlining Clinical Cancer Research: Averting a Crisis Scenario

While many of the priorities for streamlining clinical cancer research are known, there is no guarantee that the necessary changes will be carried out soon, or in a well-coordinated manner. Although ASCO and many others are working on the needed solutions, it is easy to imagine a scenario in which the full shift to an efficient, molecularly driven research system occurs only in response to crisis.

In this crisis response scenario...

Adoption of new trial designs lags throughout the next decade, even as FDA, ASCO, and other thought leaders work to establish consensus on new approaches. The costs of new cancer therapies reach new highs, though payers initially continue to cover these treatments. With relatively few incentives to invest in novel research approaches, many research sponsors continue to employ trial designs that have worked in the past.

Within a decade, however, the flow of hugely expensive drugs places an unsustainable burden on the healthcare system. Public and private payers either shift a large share of costs to patients, many of whom cannot afford to pay, or refuse coverage of new treatments altogether.

Research sponsors are then faced with a choice: Fully embrace new research approaches and lower the costs of new therapies, or exit the oncology market. For a time, the pace of discovery slows as some companies curtail their oncology operations, and promising new treatments remain untested and unavailable to patients.

Faced with this crisis, FDA, researchers, advocates and companies themselves come together to ensure the rapid adoption of new trial designs, paving the way for a new decade of progress.

This is just one of many possible scenarios. We want to hear from you: What do you think is most likely? How can such a crisis be avoided in the first place?

III. Resources—From Cost to Value in Cancer Care

The recent U.S. debate over healthcare reform has made one thing clear: Unsustainable costs are leading to fundamental shifts in the way healthcare, including cancer care, is delivered. There is a growing expectation that healthcare represent good "value," both for patients and for nations as a whole.

In oncology, this will require tackling two major challenges. First, oncology care professionals will need to adapt to demands for greater quality, efficiency and transparency in all of the care we provide. On this front, we are already leading the way by developing quality measurement and improvement approaches that are leading to better patient care.

Second, and perhaps more difficult, we will need to address the spiraling cost of new cancer therapies, particularly as novel therapies are tested and administered in combinations of two, three or more drugs. With newly approved drugs costing as much $100,000 for a course of treatment, combination therapies could quickly become out of reach for many patients and threaten the viability of cancer drug development. Solving this challenge will require dramatic shifts in the way drugs are developed and new ways of determining what constitutes value.

"In virtually all cases, the issue of cost effectiveness will increasingly be a discussion point...With rising costs, there will be an increasing challenge to say how drugs compare and contrast, and defining cost effectiveness and value."

—**Cary Adams,** *CEO, Union for International Cancer Control*

Vision for 2030

Value as the driver of oncology practice. By 2030, today's "buy and bill" model of oncology care in the U.S. will have been abandoned in the face of rising costs and new demands from patients, payers and policymakers. Instead, new payment models that promote quality and value will prevail. Specifically:

- **Routine quality measurement and improvement will be embedded firmly in oncology practice.** Aided by quality monitoring efforts like ASCO's Quality Oncology Practice Initiative (QOPI®) and by rapid learning systems such as CancerLinQ, oncology providers will know, in real time, how their care stacks up against benchmarks including guidelines and the care received by patients in other practices. Guideline adherence will be monitored continuously through patients' EHRs, and guidelines themselves will include clear quality measures and will be updated over time as insights emerge from real-time analysis of oncology practice.
- **Oncology providers will be compensated according to their ability to demonstrate value and quality.** The oncology community and payers will settle on approaches that are shown to maximize quality and patient satisfaction, while discouraging unnecessary investigation, treatments and costs. These systems will have been built upon oncologist-led quality initiatives such as CancerLinQ. As a result, both physicians and payers will accept them as a sound basis for reimbursement.
- **Oncologist training programs will teach the skills needed to ensure high-value care.** Medical school, residency and CME programs will include significant emphasis on quality measurement, data analysis, staff management and other skills that physicians will need to succeed under new practice models.
- **Public reporting of oncologists' quality of care will be routine.** Following the trend already applied to other professions, such as teaching, quality ratings for oncologists and oncology practices will be publicly available, allowing patients to judge potential providers for themselves. The oncology community will take early, proactive

"ASCO has to define metrics of success at the patient level, physician level and federal level. Issues surrounding reimbursement and research funding will be solved by accurate measures of value."

— **Dr. David Agus,** *Professor of Medicine and Engineering, University of Southern California Keck School of Medicine and the Viterbi School of Engineering; author, The End of Illness*

steps to lead the development and adoption of validated quality measures that can be applied uniformly across the oncology community.

- **Cancer care quality will be much more consistent across regions and institutions,** as quality measurement and reporting become fully embedded in oncology practice and practices adapt in response to public reporting. Where disparities still exist, health policymakers will finally have reliable information to guide their decision-making and to monitor the impact of policy changes on patient outcomes over time. Through quality guidelines and insights gained through CancerLinQ, the cost-effectiveness of care will also become much more consistent across regions.

Keeping new treatments affordable. To ensure that our expanded scientific knowledge is translated into accessible, life-saving therapies, the following shifts will occur:

- **Streamlined clinical research approaches (see Panomics section) will dramatically reduce the cost of drug development.** Adoption of new trial designs and endpoints; better understanding of how to design drugs to match molecular alterations; and greater collaboration between industry, researchers and FDA will speed clinical trials, reduce research costs and enable drug-makers to price new medicines in a range that remains accessible within the context of quality-driven reimbursement approaches.
- **Greater linkages between clinical trials and real-world care settings will increase the efficiency of research.** For example, drugs may be released into the clinic earlier in their development, based on safety data and promising signs of efficacy from early-stage trials. By measuring their impact on patient outcomes through CancerLinQ and other observational data sources, researchers could determine which combinations of drugs are worthy of the streamlined efficacy trials needed for regulatory approval.
- **Newly marketed therapies will be evaluated quickly in real-world use to guide reimbursement.** Through analysis of data collected through CancerLinQ or similar systems, both clinical guidelines and reimbursement will be settled within a short time after FDA approval—and continuously updated as new insights emerge. This will minimize the use of new agents for patients who are unlikely to benefit, providing significant cost savings.
- **The oncology community will have reached consensus on what constitutes value in new therapies.** Through the advances above, oncologists, researchers, advocates and payers will generally agree on measures that represent value, and on reimbursement mechanisms that favor high-value treatments. Drug developers will understand these criteria and prioritize new therapies with the potential to offer meaningful benefits at reasonable cost.

"In cystic fibrosis, a decision was made to make outcomes data public. There was a risk that sites would drop out of the program, but that didn't happen. Instead, providers started to devour the data. The poorly performing sites made visits to the high performers. They began to unlock the secrets. This is what happens when data is made public."

—**Dr. Atul Gawande,** *Professor of Surgery, Harvard Medical School; Professor in the Department of Health Policy and Management, Harvard School of Public Health*

"Current drug pricing is based on failure—recouping through drug sales the high costs of failed research. The challenge is to do trials better, thereby reducing costs and making pricing more affordable."

— **Dr. David Kerr,** *Professor of Cancer Medicine, University of Oxford; Past President, European Society for Medical Oncology*

Paying for quality in cancer care: New models

While this vision imagines changes over the next two decades, ASCO is already advocating for quality-driven reimbursement approaches that are patient-centered and developed in close partnership with oncologists themselves.

Through testimony before the U.S. Congress and in forums within the oncology community, ASCO has presented several care delivery models that should be explored. These include:

- Patient-centered medical homes, a team-based model that aims to provide comprehensive, continuous, high-quality care
- Case management fees that cover the full range of services oncologists provide and are tied to appropriate quality indicators
- Combination approaches involving a mix of a case management fee, clinical pathways and quality incentives

Whichever approaches are ultimately adopted, ASCO believes it is crucial that oncology providers take the lead in defining value in cancer care.

For more on ASCO's role in U.S. payment reform discussions, visit ascoaction.asco.org.

Obstacles to Overcome

Significant challenges to achieving this vision will include:

- **The potential for severe government or payer cost and utilization controls.** Policymakers and payers are under intense pressure to reign in the cost of healthcare, and may resort to approaches that limit patient choice and access to care. To head off this potential threat, the oncology community will need to quickly demonstrate leadership in improving the value of cancer care, while advocating on behalf of patients.
- **Political uncertainties.** Given the political complexities of health reform efforts, there is a risk that policymakers will delay important decisions about reimbursement, creating additional uncertainty about the future, or that they will adopt expedient approaches that harm patients and physicians.
- **Risks of public reporting of physician quality.** As we have seen in debates about public reporting in the education field, there is a risk that metrics will be poorly conceived or applied, with resulting harm to oncology practices and access to cancer care. It will be imperative for the oncology community to lead in developing these metrics.
- **Threats to drug development.** As described in the Panomics section above, revamping our nation's clinical research and laboratory systems will be complex and difficult, and companies may begin to exit the oncology market before solutions can be found. ASCO's recent Blueprint report lays out the important first steps, but the entire oncology community will need to join in achieving its recommendations.

"We need value-based reimbursement for drugs. We should be paying more for better results."

—**Dr. Mark McClellan,** *Director, Engelberg Center for Healthcare Reform, Brookings Institute*

DIALOGUE: Your Involvement

On a fundamental level, predicting the future is an impossible exercise. The vision laid out in these pages, while well-researched and carefully considered, may turn out to be off the mark in ways that we cannot imagine from where we stand today.

Yet anticipating—and preparing for—the future is an absolute necessity for the oncology field. With the number of cancer patients projected to grow dramatically in the years ahead in the U.S. and worldwide, we must do everything possible to ensure that we are well-positioned to deliver the care they will need.

This document is the starting point for an ongoing, dynamic discussion. Over the coming year, ASCO will be seeking input from you, our more than 30,000 members, to refine the vision described here. Members will have many opportunities to weigh in. These may include discussion forums on ASCOconnection.org, the professional networking site for ASCO members, as well as live discussions at state affiliate meetings and at ASCO's Annual Meeting. ASCO will periodically review and update the vision based on feedback and new developments in the oncology field.

Your input is essential. This vision is intended to be a roadmap to guide ASCO's policy and programmatic activities—and the care of patients—for many years to come. We ask you to participate actively in the discussion.

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ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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June 1, 2014

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

The Honorable Diana DeGette
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, D.C. 20515

Re: *21st Century Cures: A Call to Action* White Paper

Dear Chairman Upton and Congresswoman DeGette:

On behalf of the American Society of Nephrology (ASN) thank you for the opportunity to provide input to the Energy and Commerce Committee regarding 21st Century Cures initiative and the 21st Century Cures: A Call to Action white paper. ASN commends the Committee's for its commitment to accelerating the discovery, development, and delivery of promising new treatments to patients and stands ready to collaborate to achieve this important objective.

ASN, the world's leading organization of kidney health professionals, represents nearly 15,000 health professionals who are dedicated to treating and studying kidney disease and to improving the lives of the millions of patients it affects. ASN particularly supports efforts that bolster the ability of federal agencies and the American research and development enterprise to solve scientific challenges at every level from basic science through to care delivery.

Kidney disease affects more than 20 million Americans. There are many causes of kidney disease, but when any type of kidney disease progresses to kidney failure, patients require either dialysis or transplantation to stay alive. Currently, 600,000 Americans have complete kidney failure, called end-stage renal disease (ESRD). There are not enough organs available to transplant all of these individuals. Kidney disease disproportionately affects racial and ethnic minority populations, is associated with multiple co-morbidities including heart disease and diabetes, and is one of the most costly chronic conditions in the United States. Kidney disease worsens the outcomes of people with diabetes and heart disease and accounts for much of the mortality in individuals with diabetes. Recent data shows that kidney disease in diabetic patients continues to rise despite overall improvement in other outcomes with better management of blood sugar, suggesting controlling diabetes will not be sufficient to stop kidney disease.

As the Committee noted in its report, while America's scientific leadership has yielded important treatments for some patients, others still wait because the state of biomedical research and innovation in certain diseases is not as advanced; kidney disease is among the conditions for which we must accelerate the pace of innovation.

Although people with kidney failure requiring dialysis (ESRD) comprise less than 1 percent of Medicare beneficiaries, they account for nearly 7 percent of Medicare's budget: the Medicare ESRD Program is unique in that it covers every American with kidney failure regardless of age or income. Yet despite these staggering costs, the fundamental principles of dialysis have not changed and patients with ESRD have seen only incremental improvements in their therapy over several decades.

The 21st Century Cures initiative is a significant opportunity to spur research and development in kidney care and in other diseases where the state of biomedical research and therapies in certain diseases is not as advanced.

Discovery

The United States' position as the global leader in basic and clinical research is the result of a strong history of leadership from the National Institutes of Health (NIH), academic medical centers, industry, and other federally-funded research agencies, and ASN shares the Committee's belief that maintaining that position is an important goal. Continuation of robust federal funding for the NIH and other federally-funded research agencies, such as the NIH, the Department of Veterans Affairs (VA), and Patient Centered Outcomes Research Institute (PCORI) is the crucial cornerstone to achieving this objective. Ensuring funding at the NIH and other research agencies is necessary not only to sustain the important ongoing work of today's scientists but also to make careers in biomedical research attractive to the next generation of investigators.

The number of U.S. medical graduates pursuing careers as physician-scientists is declining.. The percentage of physicians engaged in research as their major professional activity in the United States has decreased from a peak of 4.6 percent in 1985 to 1.8 percent in 2003, a trend that has only worsened in the last decade. Unless we continue to invest in biomedical research and make careers in this field viable, America will not only develop fewer new discoveries and cures, but also lacking the human capital to do so and defend our leadership role in the longer term.

In addition to traditional federal funding for investigator-initiated research, public-private partnerships and other creative funding mechanisms can also further the discovery process. For instance, while not a substitute for traditional investments in federal research agencies, prize competitions can serve a complementary role spurring scientific and technologic breakthroughs. Unlike traditional research funding models, competitions have the added benefit that the prize is only paid-out if a competitor wins. Moreover, competitions also typically draw competitors from outside the traditionally interested in the disease state or biomedical problem, broadening the scope of innovators and drawing on the creativity of multiple disciplines.

Promoting coordination and collaboration across federal research agencies, such as between NIH, PCORI, and the VA to ensure aligned priorities and sharing of resources and information is one strategy that can help achieve this goal. Similarly, encouraging collaboration between NIH Institute-Centers can make effective use of resources and advance understanding in areas of shared interest.

Encouraging funding mechanisms that promote efficient use of data by making datasets open and accessible for use by other investigators is another strategy to better disseminate knowledge and create opportunity for discovery.

In certain areas, a better understanding at the molecular level about what biological mechanisms trigger the onset or proliferation of a particular condition or disease exists. For instance, NIH-supported investigators recently identified that African Americans with the APOL1 gene are at substantially higher risk for kidney failure. Supporting further investigation and translational research in areas where promising genetic data exist—such APOL1—is especially important to transform these clues into the cures of the future.

Development and Delivery

As the Committee observes in its report, the size, failure rates, and costs of conducting trials—as well as administrative and regulatory burdens—are at all-time highs. While the randomized, double-blinded, placebo-controlled model remains the gold standard, ASN believes that increasing the adoption of pragmatic clinical trial designs, and encouraging more creative and cost-efficient trial designs, is an appropriate strategy for certain types of research. While recognizing that not every trial is appropriate for alternative trial design, ASN supports exploring creative, cost-effective approaches that maintain scientific integrity and patient safety.

Importantly, movement toward novel trial designs must be inclusive, involving NIH (or other federal research agencies), industry, and FDA. CMS, which will ultimately determine coverage, and should also be included in early in considerations regarding how new products will be evaluated.

Beyond pragmatic clinical trial design, creation of new, clearly defined endpoints is an important step in making the development of new products feasible and cost-effective. In particular, ASN supports the Food and Drug Administration's (FDA) efforts on several fronts to incorporate the patient perspective in the approval process. The society encourages the Committee to prioritize this type of engagement when considering ways to accelerate treatments that are of greatest value from the patient perspective.

ASN would also like to highlight the value of its public-private partnership with the FDA, the Kidney Health Initiative (KHI). The mission of KHI is to advance scientific understanding of the kidney health and patient safety implications of new and existing medical products used for to treat other conditions and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products.

Since its inception in 2012, KHI has served as a valuable forum to bring together patient groups, health professionals, and drug, device, and biologic manufacturers with FDA to identify and tackle barriers to the development of new therapeutics and ensure the safety of drugs, devices, biologics, and food products for patients with kidney disease. Nearly 70 companies and organizations joined KHI in its inaugural year, highlighting the stakeholder interest in and need for greater collaboration and partnership with the FDA.

This successful public-private partnership is a testament to the FDA's active participation with the kidney community and to the power of such collaborations to help accelerate the development of therapies and address unmet medical needs for Americans affected by kidney disease. Importantly, KHI has already identified many of the barriers to entering the kidney space and bringing new therapeutics to market, and is working with the FDA to find mechanisms to overcome these barriers. ASN believes that KHI can serve as a model for other areas of medicine that seek to catalyze innovation and attract investment in new therapies.

Conclusion

ASN applauds the Committee for its work on this initiative and its commitment to ensuring that the United States continues its preeminence in the discovery, development, and delivery cycle and thus, remains the world leader in innovation. The society is grateful for the opportunity to provide input now and throughout the ongoing initiative and hopes this feedback is helpful.

Again, thank you for your time and consideration. To discuss ASN's input, the Kidney Health Initiative, or any other issues related to kidney research, please contact ASN Manager of Policy and Government Affairs Rachel Meyer at meyer@asn-online.org or at (202) 640-4659.

Sincerely,

Sharon M. Moe, MD, FASN
President

THE RACE TO YES

SAFE + EFFECTIVE = YES!

INTRODUCTION

We applaud the Committee on undertaking the 21st Century Cures Initiative. The status quo for discovering, developing, and delivering treatments is failing the rare disease community. We welcome the opportunity to offer our input on behalf of The Race to Yes.

The Race to Yes is a very recent and current effort, formed in December of last year, with the initial purpose of convincing the FDA to provide guidance for accelerated approval for the first-ever treatment for Duchenne Muscular Dystrophy, a rare, universally fatal childhood disease that is the leading genetic killer of children. Duchenne is a devastating, unimaginably brutal disease that robs children of their muscle function, and eventually costs them their lives. Children with Duchenne will need help going to the bathroom at the age when most kids are getting their driver's license. They will lose the ability to feed and care for themselves. The will endure countless dangerous surgeries to relieve pain. And after only a few precious years, they will leave an empty seat at the dinner table.

The Race to Yes has a mandate – to do everything possible to persuade the FDA to act quickly on behalf of these children. As a direct result of our efforts, in April, the FDA finally relented and provided guidance to the company developing this promising therapy. But what we went through to get there is proof beyond any reasonable doubt that the current system, despite the tools provided to the FDA by Congress, does not work in the best interests of patients, and the need for change is immediate and urgent.

It's one thing to hope and wait for a treatment that has not yet been developed. But when the treatment exists and it remains out of patients' reach because of bureaucratic hurdles that block the way, that is wrong. Given the investments made by your Committee in early scientific discovery into diseases like Duchenne through the National Institutes of Health, how can we tolerate a system where those investments are left to languish just short of the finish line of the drug approval process? Your Committee and Congress recognized this challenge when you passed the Food and Drug Safety and Innovation Act (FDASIA) and codified the standard that promising drugs for rare and fatal diseases with no other treatment options can be granted conditional approval while additional testing is carried out to confirm initial indications of safety and efficacy. Like so many other rare diseases, Duchenne has no treatment and no cure, and Duchenne patients have had very little reason to hope – until recently.

A company has been developing a promising therapy for Duchenne called eteplirsen, and by the fall of 2012 had clinical data showing production of novel dystrophin in 100 percent of the 12 patients in the study. In addition to this biomarker data, the study results demonstrated that the kids on the drug fared better clinically than the kids on placebo. While the trial was small and therefore not statistically powered to determine clinical benefit, the efficacy trend was pronounced.

With the passage of FDASIA and its emphasis on applying existing authority for Accelerated Approval to rare and orphan diseases in the same way it was leveraged for HIV and cancer, members of the patient community mobilized in early 2013 to meet with the FDA to communicate that Duchenne was a perfect candidate to benefit from Accelerated Approval and that the results from eteplirsen studies warranted its broader use. The FDA was receptive and in July 2013, the company developing eteplirsen announced that, based on FDA feedback, they would be submitting a New Drug Application before the end of 2013.

But then in November, the FDA inexplicably reversed its position and indicated that before considering even conditional approval, the agency was likely to require a large-scale, placebo-controlled trial. This traditional regulatory path would result in years of delay. Children with Duchenne who could directly benefit from this drug would instead lose their ability to walk and possibly die before getting access to a treatment that had shown a high degree of probability that it would slow the progression of the disease.

We rely on the FDA to expedite, not further drag out, the process of developing safe and effective drugs for our children. The law states that the FDA should be flexible when considering approval of drugs for rare, fatal diseases. But just because you've passed a law doesn't mean it is automatically or consistently followed. As your Committee knows, it takes hard work and significant advocacy and education to change cultures and mindsets to bring them in line with both necessity and the law. Our advocacy campaign was aimed at urging our government to do its job and to do it efficiently, to act on a promising therapy for a rare, fatal childhood disease – a therapy with no adverse effects and significant evidence of efficacy in a population that faces progressive loss of muscle function and certain death at an early age. Nevertheless, patients were needlessly forced to wait for months upon months for action.

There are plenty of disincentives to pushing for change within our existing approval process. The Race to Yes was warned repeatedly that trying to pressure the FDA would backfire and cause the agency to dig in its heels even more. We were not

deterred. We will not be deterred as long as our children's lives hang in the balance and there is something we can do – and that the government should do – to help.

Given our direct and recent experience, it comes as no surprise to us, and should not be surprising to your Committee, that so-called "Right to Try" laws are sweeping the country, that requests for compassionate use are exploding, or that companies are turning to the European regulatory system for earlier approvals. The U.S. system is unreliable and inconsistent, plagued by failures and refusals to communicate, subject to inexplicable and costly delays, and lacking disease-specific expertise and experience. Worse still, there are the implied threats of retribution for pushing too hard and too often the outright dismissal of the patient voice as uneducated on the process and ignorant on the science.

We realized after too many months of delay that it was going to take something extraordinary to get the FDA to move. Many of us have been working for years to encourage action. But we believed an unprecedented, concerted effort was necessary. That is when we as patient advocates formed the Race to Yes. The Race to Yes is a movement and a call to action to change the mindset at the FDA that has failed to evolve consistent with the science and that all therapies should be treated the same. Our goal is simple: to break down the many unnecessary barriers that exist to developing and gaining access to and approval for treatments for rare diseases. We initiated the following actions:

- Launched a formal White House petition to appeal to the FDA's boss, the President of the United States, to urge the FDA to act. On the first day of our petition drive, we tapped most of our families and friends and cobbled together only 500 signatures. We were competing on the White House petition site with a paid-for petition to make baseball's opening day a National Holiday. How would we get stadiums of people to sign our rare disease petition – and do so within the 30-day deadline that would guarantee a response? We mobilized on all fronts, in our communities, at work, at school, online. And we appealed to people well beyond the Duchenne community, people who saw a broken system and who wanted to see it fixed. Amazingly, we succeeded in getting more than the required 100,000 signatures in 26 days in March.
- Brought the world's leading scientists to the meet with the FDA. The scientists came from all over the world. In the 90 minutes we were granted by the FDA, these scientists reviewed both the safety and efficacy data that merited accelerated approval.
- Came to Capitol Hill with these scientists and briefed 100 Members of Congress and congressional staff.

- Sought your help to question the FDA regarding FDASIA and its application to Duchenne muscular dystrophy directly in letters, meetings, and hearings,
- Asked concerned persons to send letters, make phone calls, and transmit emails directly to the FDA.
- Shared our stories with the news media, on CNN, Huffington Post, Fox News, the Washington Post, and in major and local papers and TV stations from coast to coast.
- Repeatedly pressed the company and FDA officials for timelines, for feedback on outstanding issues, and for any shred of information they could share or information on when they would make a decision on how the company could move forward.

Finally, in April of this year, the company announced that the FDA had provided guidance on how they could proceed on eteplirsen, as well as very limited guidance on follow-on therapies. The path forward defined by the FDA will eventually allow for boys around the country to access eteplirsen while the definitive answers needed through further study are collected and without the need for a placebo-arm. While we are pleased that FDA has provided this guidance, it is what we have been requesting from the beginning and what was merited as early as the fall of 2012. And while we are gratified to have achieved this outcome, it has come with a price: lives lost for children who died while waiting for access to this drug; and for countless other children, function lost, including the ability to walk, climb stairs, hug their parents, and pull up their blankets up at night. As parents, our daily lives were consumed and exhausted by the efforts noted above to get the attention and action of the FDA, all while caring for boys suffering from Duchenne. These extraordinary efforts and campaign-style tactics should not have been necessary, but they were. Until the system is fixed, they'll be required over and over again.

RECOMMENDATIONS

As the Committee seeks and receives recommendations for how to improve the existing process and keep America the global leader in developing treatments and cures, we should start by looking at what the goal is – quick approval for safe, effective therapies for diseases – and work backward to figure out the best way to get us there. To that end, we wanted to share some specific answers to questions raised in your White Paper.

"[A]re there areas or opportunities where the agency is not using [expedited review] authorities to their maximum potential where it should be?"

The FDA is not using expedited review and accelerated approval authorities to their maximum potential. If it was, it would have given guidance regarding eteplirsen almost a year ago. The culture must change.

The path forward for eteplirsen is about so much more than this one specific drug. It's about creating a new culture, about opening doors and blasting through walls when there aren't any doors. We believe that in eteplirsen's specific case, future therapies that use the same mechanism – exon-skipping – should automatically be put on the same accelerated approval track. We believe the FDA should apply this notion to any promising treatment for a rare disease that is based on the same chemistry as a previously approved treatment, implementing a policy of "platform approval." There is no reason to make the next treatment start over at square one.

"Is the FDA structured and managed to enable the agency to rapidly incorporate innovative new approaches and technologies in its review processes?"

The FDA currently is not structured and managed in a way that facilitates rapid review of treatments for rare, multidisciplinary diseases, and certainly is not structured to "rapidly incorporate innovative new approaches." The FDA must improve its internal communication and collaboration among its own offices and divisions to ensure everyone who should play a role in the regulatory process for each specific treatment is included. For example, eteplirsen is in the hands of the Division of Neurology. The Office of Orphan Products Development should be much more involved, and we have had to beg the Division of Ethics to get involved and communicate with the Division of Neurology on this treatment. For all treatments, but especially those for rare diseases, from the very start of communication with the drug sponsor, there should be automatic representation from ALL offices and divisions that should play a role in regulating a particular drug's development.

"What roles can NIH and other outside experts play in the process?"

In the case of Duchenne, there are relatively few clinical experts. None of them work for the FDA. The FDA needs to implement a process in which the most qualified independent clinical experts are consulted and encouraged to share their knowledge at every step of the process. In addition, members of advisory committees and review panels must be required to have some baseline knowledge of the disease in question.

The FDA also needs to collaborate more effectively with patient experts. To be clear, we are not ancillary to the process. We are parents of children subjected to invasive surgical procedures in the name of science and drug development. We are, by painful

necessity, smart on the disease and the process. We are significant financial investors. Our children are the end-users. And we are taxpayers. Our role in this process is significant, and the FDA must give us a seat at the table, not lip-service and platitudes. To work well, the process must include reliable dialogue that informs and ensures consideration of relevant information, and that leads to transparent, accountable, sound, and timely decision making. The FDA should not be allowed to hide behind a proprietary curtain to shield substantive communication with patient experts, who may be the only people who have enough knowledge about the disease to accurately evaluate a potential treatment.

"[I]s the randomized, double-blinded, placebo-controlled [trial] model the best approach in all cases?"

The answer is a resounding NO. In the modern age of developing medicines for rarer and more specific forms of diseases, this model no longer applies, and actually unnecessarily harms people. Particularly in the case of rare diseases, the small patient population often cannot reasonably support a traditional trial design. Several considerations should inform the design of a trial, including but not limited to:

- First, the risks to trial participants, both to the participants who are on the treatment, and those who may be on a placebo. In the case of Duchenne, participants who receive the placebo must still undergo painful muscle biopsies – losing muscle and function that they will never get back – without any potential benefit from the therapy being evaluated. The natural history of Duchenne is well understood by the clinical and patient experts. Ethically and clinically, requiring a placebo-controlled trial in this case is unwarranted.

- Second, the size and makeup of the patient population. In the case of Duchenne and other rare diseases, the size of the patient population simply cannot support a traditional trial design. There is a finite number of patients with this disease. Every potential treatment must be evaluated using this same population. There must be an acknowledgement that a traditional large scale trial may be impossible and alternative models must be identified.

- Third, whether the alternative – progressive loss of muscle function and death at a young age, in the case of Duchenne – is worse than any side effects that may occur. The benefit-risk calculation is and must be vastly different for rare, fatal diseases. Particularly in cases where there is no existing treatment and strong evidence of safety and efficacy in a treatment under development, we must err on the side of giving earliest possible access to patients who want it.

- Fourth, too often it seems that regulators are overly focused on the process by which the evidence of efficacy and safety was collected rather than on the data itself. We must urge regulators not to ask, "Does the process by which this data was collected conform to the traditional methodology I am used to?" but rather, "Does this data answer my question? If not, what additional data do I need?" As you note in your White Paper, this is a historic moment in time for scientific advancements. Americans have a chance to take advantage of this miraculous progress and as a result live longer, healthier lives. To grasp that opportunity and ensure that these advancements bring to bear real improvements in the lives of real people, we must make sure that the science serves the patients and not the other way around.

CONCLUSION

We are grateful for the opportunity to share our views and we are especially grateful that you are listening. We hope you will carefully consider our recent and direct experience with the existing drug approval process, and that you will use us as a resource as this initiative moves forward. We look forward to working with you.

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Generic Pharmaceutical Association

GPhA Comments to "21st Century Cures: A Call to Action"

The Generic Pharmaceutical Association (GPhA) appreciates the opportunity to provide comments regarding the May 1st white paper, "21st Century Cures: A Call to Action." GPhA's core purpose is to improve the lives of patients by providing timely access to affordable pharmaceuticals. We applaud the Committee for the 21st Century Cures initiative and look forward to working with you to accelerate patient access to life-saving cures.

Our member companies manufacture more than 90% of all generic pharmaceuticals dispensed in the United States, and their products fill nearly three billon prescriptions per year. Members of GPhA have also produced safe and effective biosimilars for sale outside the United States for more than seven years. Today's generic industry is innovative – from the processes used to manufacture generic drugs, to the new methods of delivering high-quality products, to the development of innovative, less costly ways of bringing biologics to patients with biosimilars. This innovation will only continue in the future as more complex generic drugs and biosimilars come onto the market.

Competition Drives Innovation

As the "Call to Action" white paper notes, "It is clear that the discovery, development, and delivery process is a cycle…the country that fully embraces the entirety of this cycle will be the innovation leader for the 21st Century." The competition in the pharmaceutical marketplace currently provided by generic drugs – and the competition that will soon be provided by biosimilars – is an important part of that cycle and is vital in both assuring patient access to life-saving cures and in spurring innovation and research into new cures, both brand and generic. Innovative does not have to mean more expensive, and ensuring that patients have affordable access to innovative treatments should be an integral aspect of the conversation around 21st Century Cures. Even the best of medicines are of no value if their high cost puts them out of reach for patients who need them.

This year, we commemorate the 30th anniversary of the Hatch-Waxman Act, the bipartisan compromise signed into law in 1984 that created the modern generic drug industry. The law struck a delicate balance between fostering competition and rewarding innovation. In the past 30 years, generic utilization in the United States increased from only 20% in the mid-1980s to 84% today. According to IMS Health, in the past decade generic drugs have saved the U.S. health care system more than $1.2 trillion.

The enactment of Hatch-Waxman was also a catalyst for investments in research and development by brand pharmaceutical manufacturers. The Congressional Budget Office has noted that since the law's enactment in 1984, private sector spending on research and development increased from $8 billion to $50 billion in 2008, with annual increases of

approximately 9% per year.[1] It is the law's balanced approach of looking at the entire life cycle of a product that has been so successful in promoting both innovation and access for patients, and it is that balance that should be maintained as the Committee develops new legislative proposals to expand on those goals.

Generic manufacturers are at the forefront of innovation into new affordable treatment options, particularly in the area of biosimilar development. GPhA member companies currently manufacture biosimilars in highly regulated markets around the world, including the European Union, Canada, Australia, and Japan. Capturing the opportunity to make lifesaving biologic medicines available to millions of patients at lower cost is a priority objective for our industry, and generic manufacturers are working actively in this field.

Generic manufacturers not only increase patient access to life saving therapies at lower costs, but also play a critical role in adequately supplying the market and preventing drug shortages. Generic manufacturers' expertise and capacity in the sophisticated, high-quality manufacturing of small molecule, biosimilars, and complex small molecule products is increasingly essential in guaranteeing access to treatment for the most vulnerable of patient populations

Biosimilars

It is predicted that by 2016, eight of the top 10 drugs on the market will be biologics.[2] Biologic medicines are often the only lifesaving treatments for the most severe diseases, but their high price tag can keep them out of reach for many patients. The average daily cost of a brand name biologic product is approximately 22 times greater than a traditional drug.[3]

The cost of biologics is increasing at a faster annual pace than any other component in health care. As proven with chemical prescription drugs, biosimilar competition is expected to be the most important opportunity to hold down the cost of biologic medicines. The most effective way to make biologic products available to more patients is through an effective biosimilars pathway.

GPhA is working with the FDA to ensure that the approval process for biosimilars is workable and provides for timely availability of FDA-approved, safe, effective, and less-costly biosimilar medicines. GPhA has pushed for a scientifically feasible regulatory scheme that ensures patient safety and is not a barrier to competition. Robust competition is needed to lower costs, increase patient access, and spur future innovation.

GPhA recommends that all biosimilars approved by the agency share the same international non-proprietary name (INN) as the biologic products to which they refer, because the statutory standard for approval is to be "highly similar" and have "no clinically meaningful differences" to the reference biologic. Last year, GPhA filed a citizen petition with the FDA detailing its

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[1] Congressional Budget Office, Economic and Budget Issue Brief, "Pharmaceutical R&D and the Evolving Market for Prescription Drugs," October 26, 2009.
[2] Statement of John D. Ludwig, Pfizer. http://www.future-science.com/doi/pdf/10.4155/tde.11.58
[3] Hilary Krame, Why Biologics Remain Expensive, *Forbes* (2009). http://www.forbes.com/2009/12/03/kramer-health-care-intelligent-investing-pharmaceuticals.html

position on biosimilar naming.[4] The adoption of unique non-proprietary names for each biosimilar could jeopardize patient safety, inhibit market competition, and disrupt the current global naming system. Added layers of suffixes and prefixes will cause unnecessary confusion among patients and providers. Confusion would also unduly influence the marketplace and impede competition, reducing the ability of patients to receive biologic medicines at a lower cost. The GPhA petition holds that the global INN system to keep patients safe, which has been in place for 50 years and used in scores of countries around the world, should not be changed for one subset class of products. Doing so would reduce the number of biosimilars available to patients and inhibit patient access to these cures.

Restricted Access

The Food and Drug Administration Amendments Act of 2007 (FDAAA) gave FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of a drug or biological product outweigh its risks. Certain drug manufacturers have been using tactics that initially grew out of REMS Elements To Assure Safe Use (ETASU) requirements to delay generic competition for REMS and non-REMS products alike. Specifically, manufacturers are employing restricted distribution networks to deny manufacturers of generics and biosimilars access to product samples they need to obtain FDA approval and market entry. Certain manufacturers also are developing additional ways to abuse REMS programs to prevent and delay generic competition, including exploitation of the statutory presumption that brands and generics develop a single-shared REMS program.

The abuses are growing, and the resulting delay in generic and biosimilar competition is negatively affecting patient access to life-saving medicines. Both the FDA and the Federal Trade Commission (FTC) have taken steps to ameliorate abuses, but legislation is needed to close this loophole that is inhibiting generic manufacture research into new generics and biosimilars and delaying patient access to life-saving, affordable cures.

Food and Drug Administration (FDA) Funding

Given the critical mission of the FDA to protect the public health, it is vital that the agency have the resources necessary to assure timely patient access to both brand and generic medicines. Bringing a generic drug to market requires extensive research and development by manufacturers that can take upward of 18 months to complete and cost millions of dollars. The FDA's demanding generic review and approval procedures for generic drug applications are the gold standard for regulatory agencies around the world. GPhA supports providing the FDA with the appropriations needed to assure a timely and predictable generic approval process so that patients have access to generic medicines.

User fee programs are also instrumental in the shared effort by FDA and the generic industry to help patients gain timely access to more affordable generic medicines and biosimilars. GPhA remains strongly committed to the Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BSUFA) that were enacted in 2012. We also support legislation to assure that

[4] GPhA Citizen Petition to FDA, September 17, 2013, http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-1153-0001

FDA user fees are not subject to sequestration in future years, which would delay patient access to live-saving generic treatments.

Biosimilars represent a major emerging opportunity to deliver high-quality medicines to patients and lower costs for the government and other payors. GPhA believes that Congress should allocate funds to FDA for a consumer education campaign about the science and benefits of biosimilar medicines to help drive patient understanding of these new medicines. This campaign will further the public health goals of the FDA and help alleviate the strain on federal spending.

Timely and Predictable Generic Drug Approval Process

The generic pharmaceutical industry and the FDA share the view that GDUFA and its obligations are a public health priority. GPhA commends the FDA for committing to making the Abbreviated New Drug Application (ANDA) process more timely and predictable and for taking the appropriate steps to meet GDUFA goals, which will be measured in years 3-5.

In January 2014, FDA demonstrated its commitment to continuous improvement of the approval process by announcing communication enhancements to the ANDA review process. These changes are positive steps that can make it significantly easier for industry to assess the status of submissions and improve market launch planning. FDA is also working quickly to achieve its commitment under GDUFA to reduce the backlog of generic drug applications at FDA. As the agency does so, it is vital that first-to-market applications be approved by the first day of patent expiry so that patient access is not unnecessarily delayed.

GPhA will continue working with the Committee and the FDA to improve process transparency and assure that patients gain timely access to more affordable medicines.

National Institutes of Health (NIH) Funding

GPhA and its member companies strongly support federally funded investments in biomedical research at the National Institutes of Health to ensure that the United States remains at the forefront in innovation and discovery, and we oppose reductions in critical NIH funding. Inadequate funding would jeopardize scientific discovery and economic growth. This includes basic research – basic scientific research that advances the frontiers of knowledge is necessary and should be supported by the federal government. As the participants in the May 6th roundtable unanimously agreed, assuring that NIH has the resources needed to maintain that leadership is vital to ensuring that patients have access to life-saving cures. GPhA and the generic industry stand ready to work with members of the Committee on both sides of the aisle in achieving that goal.

Incentives for Development

GPhA looks forward to working with the Committee on examining the incentives for investment in biomedical research and the development of new drugs and biologics. U.S. pharmaceutical intellectual property laws strive to maintain a balance between protecting intellectual property and promoting access to affordable generic medicines. GPhA has member companies that

manufacture both brand and generic products, so we understand the importance of a balanced approach that fosters both innovation and competition. Any legislative proposals should avoid needless intellectual property incentives that would act as barriers to generic competition, which has proven to be a driver of new drug innovation, and thereby create an incentive for inefficient and non-innovative research and development. The goal should be for companies to direct funding to the innovative discovery of new cures rather than rewarding the development of non-innovative, "me too" products.

Conclusion

GPhA appreciates the opportunity to provide comments on opportunities to assure patient access to affordable, life-saving cures. We look forward to working with the Committee on this important initiative and developing legislation to achieve our shared goals.

Genetics Society of America

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May 30, 2014

21st Century Cures Initiative
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, DC 20515
cures@mail.house.gov

Dear Chairman Upton and Colleagues:

We are writing on behalf of the Genetics Society of America (GSA), a professional scientific society with more than 5,000 members working to deepen our understanding of the living world by advancing the field of genetics, from the molecular to the population level.

Thank you for the opportunity to provide input on your deliberations about health research through the 21st Century Cures Initiative. GSA shares your concern about the need to accelerate the pace of cures in America and the critical need to enhance our investment in the research that provides the foundation for medical treatments. Modern approaches to medicine increasingly rely upon an understanding of the complex processes that underpin both health and disease—and which are shared across many living systems.

GSA represents scientists from all 50 states, united by a focus on understanding the operation of living systems. Many of our members do not work directly in humans, but in experimentally accessible model organisms including fruit flies, roundworms, baker's yeast, zebrafish, and many other systems. The fundamental knowledge learned from these non-human systems is *essential* for advancing our understanding of human disease. Indeed, a significant proportion of the genes implicated in human disease were first discovered and characterized in these model systems. As such, studies in model organisms are crucial for the development of new drugs and therapies, even though it may be many years before those treatments come to market. Moreover, the perfect balance of intellectual adventure with uncompromising standards of rigor that comes from training with model organisms hones the skills of the next generation of researchers.

The mission of *21st Century Cures: A Call to Action* states that you plan to look at the full arc of the innovation cycle—from discovery to development to delivery. GSA especially wishes to focus on the importance of discovery. Despite all that we are learning from our previous and ongoing investments in biomedical research, there is much more to discover in the biological sciences that will impact treatments and cures in the future. Although the white paper appropriately includes the challenges related to development and delivery of drugs, we emphasize that *without discovery, the other stages*

will not follow. Translational research simply cannot occur without a base of new knowledge and understanding of underlying biological mechanisms to translate. At a time of exceptional promise, we are concerned that declining investments in foundational research today will lead to a dry pipeline down the road.

The power and potential of basic research is rooted in its unpredictability, since it is impossible to foresee the source of the next major breakthrough.

As an example, the whole of the biotechnology field relies on the use of restriction enzymes—proteins that cut DNA at defined locations. Our understanding of restriction enzymes emerged from foundational research in bacterial systems. Thus, the entire multi-billion-dollar biotechnology industry would not exist without the previous investment in this fundamental work. The discovery of restriction enzymes has also directly led to medical advances, such as the cost-effective and accessible production of insulin, which has revolutionized the treatment of diabetes.

The completion of the Human Genome Project, likewise, has laid the groundwork for understanding the impact of genetic variation on disease, which is critical as researchers work to decode the genetic factors contributing to such complex conditions as Alzheimer's disease, cancer, schizophrenia, diabetes, and Parkinson's disease. Moreover, the Human Genome Project itself led to the development of technologies that have reduced the cost of sequencing a human genome by a factor of nearly one million. The promise of personalized precision medicine is only possible because genome sequencing is becoming an affordable and routine clinical test. The vast amount of data collected as part of the Human Genome Project also spawned entire new fields—including bioinformatics and computational biology—which, when combined with prior developments in population genetics, are now central to the way that we approach the genetics of disease.

Recent developments also demonstrate the contributions of model organisms. For example, the excitement from the ability to edit the human genome precisely, which shows promise in curing individuals of AIDS, is derived directly from genetic studies of recombination in bacteria, yeast, and *Drosophila*—and curiosity-driven research on how certain bacteria handle infection. Similarly, fundamental discoveries in *C. elegans* and plants revealed the unexpected phenomenon of RNA interface, which shows potential for clinical use in regulating gene activity.

These examples demonstrate that it is only through support for a broad spectrum of high quality and promising research, as vetted by experts in the field, that we can lay the foundation for the future.

Although the private sector plays an important role in drug development, basic research necessarily depends upon public investment. Indeed, private industry relies upon the fruits of publicly-funded research. Without robust federal funding from the National Institutes of Health, National Science Foundation, and other federal agencies, the building blocks for innovation will not be available. And

without that foundation, the nation will lose its place in innovation, in the development of medical treatments, in the creation of private-sector biomedical companies, and in the economic return that will result.

Thank you again for the opportunity to participate in your discussions.

Sincerely,

[redacted]

Vicki L. Chandler, PhD
President

[redacted]

Michael Lynch, PhD
Immediate Past President

[redacted]

Jasper Rine, PhD
Vice-President / President-Elect

Genetics Society of America

ABOUT GSA: Founded in 1931, the Genetics Society of America (GSA) is a professional scientific society with more than 5,000 members worldwide working to deepen our understanding of the living world by advancing the field of genetics, from the molecular to the population level. GSA promotes research and fosters communication through a number of GSA-sponsored conferences including regular meetings that focus on particular model organisms. GSA publishes two peer-edited scholarly journals: *GENETICS*, which has published high quality original research across the breadth of the field since 1916, and *G3: Genes|Genomes|Genetics*, an open-access journal launched in 2011 to disseminate high quality foundational research in genetics and genomics. The Society also has a deep commitment to education and fostering the next generation of scholars in the field. For more information about GSA, please visit www.genetics-gsa.org. Also follow GSA on Facebook at facebook.com/GeneticsGSA and on Twitter @GeneticsGSA.

PPTA
Plasma Protein Therapeutics Association

June 1, 2014

The Honorable Fred Upton
The Honorable Diana DeGette
Committee on Energy & Commerce
2125 Rayburn House Office Building
Washington, DC 20515

Re: *21st Century Cures: A Call to Action*

The Plasma Protein Therapeutics Association (PPTA) appreciates the opportunity to comment on the Energy and Commerce Committee's 21st Century Cures initiative ("the Initiative"). PPTA supports the goal of enhancing regulations to improve the innovation continuum and "accelerat[ing] the discovery, development, and delivery of promising new treatments to patients,"[1] and appreciates your leadership in convening and guiding this important conversation.

PPTA represents the innovators and manufacturers of plasma-derived therapies predominantly used to treat rare, chronic and life-threatening diseases and disorders, including alpha-1 proteinase inhibitor deficiency, hemophilia, von willebrand disease, and primary immune deficiency (PID) diseases. Therapies include albumin, $alpha_1$-proteinase inhibitor, antithrombin III, plasma-derived and recombinant blood clotting factors,[2] C1 esterase inhibitor, fibrin sealant, immune globulin, hyperimmune immune globulin, prothrombin complex concentrate, and protein C concentrate.[3] Collectively, these therapies are known as "plasma protein therapies." PPTA's U.S. manufacturer membership includes Baxter BioScience, Biotest, CSL Behring, Grifols, and Kedrion.

Overview: Unique by Nature

Plasma protein therapies comprise a unique class of biologics within the biopharmaceutical industry. From the human-derived plasma starting material, through the complex manufacturing process, to final physician-administration, plasma protein therapies and the rare disease patients that rely on these therapies for their lifesaving treatment consistently face distinct challenges and particular regulatory treatment. For example, nearly all plasma protein therapies treat rare diseases, and certain therapies treat extremely rare diseases that feature prevalencies of fewer than 100 patients. The

[1] Energy and Commerce Committee, *21st Century Cures: A Call to Action* (May 1, 2014).

[2] Recombinant blood clotting factor therapies are those created using recombinant DNA technologies, which entail the integration of genes coding for the production of human blood clotting factor proteins into laboratory cell cultures. The cell cultures produce the blood clotting factor proteins, which are subsequently collected, purified, and further refined into safe and effective biologic medicines.

[3] Human plasma is the clear liquid portion of blood that remains after the red cells, leukocytes, and platelets are removed. Due to its human origin, complexity, and richness in therapeutically useful proteins, human plasma is a unique biological material. *See* Thierry Burnouf, *Plasma Proteins: Unique Biopharmaceuticals – Unique Economics*, *in* 7 PHARMACEUTICALS POLICY AND LAW, BLOOD, PLASMA AND PLASMA PROTEINS: A UNIQUE CONTRIBUTION TO MODERN HEALTHCARE 209 (2005, 2006).

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rare nature of the disease states targeted and treated by plasma protein therapies often presents unique research, development, and regulatory challenges. Additionally, manufacturers employ different fractionation processes to derive each distinct brand within the plasma protein therapeutic class. Due to the distinct manufacturing processes used by the industry, plasma protein therapies are non-interchangeable, sole source biologics that produce different therapeutic outcomes on a patient-by-patient basis. As a result of the therapies' non-interchangeable nature, patients depend on appropriate, timely, and uninterrupted access to all brands within a therapeutic class to be assured that they are able to identify and become stabilized on the therapy that best fits their health status.

The industry is further differentiated by the reliance on human donated plasma as the starting material for therapeutic production. The collection of human donated plasma from 430 collection centers dispersed across the United States is a time- and resource-intensive system that adds multiple layers of complexity and regulation, resulting in a 7-9 month production process. Notably, because each plasma donation only contains a fraction of the necessary proteins to produce a given therapy, there is an inherently finite supply of therapies. For example, it requires approximately 900 donations to provide enough alpha-1 proteinase inhibitor to treat one alpha-1 antitrypsin deficiency patient for one year. Importantly, however, the finite supply of therapies does not mean that therapies are in shortage or that patients are unable to access their lifesaving treatments, but rather underscores the need for regulations and reimbursement mechanisms to protect patient access to these therapies.

PPTA greatly appreciates the opportunity to provide the industry's unique perspective on the current state of the discovery-to-delivery innovation continuum and offer solutions aimed at engendering future innovation and improving the state of patient access.

Summary of Recommendations:

- **Payment and Delivery**
  - Ensure that payment and reimbursement policies incentivize innovation and maintain patient access; and
  - Expand regular stakeholder engagement by the Centers for Medicare and Medicaid Services (CMS) to advance payment methodologies that keep pace with innovation and the development and commercialization of new technologies.
- **Discovery**
  - Increase and stabilize public funding for basic scientific research; and
  - Mitigate barriers that continue to impede the development of a robust body of research focused on rare diseases.
- **Clinical Development**
  - Improve regulatory predictability through timely rulemaking procedures.

PPTA strongly supports the Committee's efforts to improve the state of innovation and patient access, and encourages the Committee to continue to engage all stakeholders in a transparent manner and to maintain patients, health outcomes, and quality of care at the center of the discussion.

I. DELIVERY AND PAYMENT

While the Committee's White Paper examined the barriers to innovation on the continuum from discovery to delivery, payment plays a critical and determinative role in driving innovation and patient access to care. Importantly, even if steps are taken to increase the efficiency of pathways to bring products to market, without effective reimbursement models, innovators will face headwinds and patients will experience access challenges. Accordingly, as the Committee reviews and amends payment policies to improve the sustainability of the healthcare system, PPTA recommends that payment-related proposals also be examined for the potential to impact innovation and patient access to care.

1. Ensure that Payment and Reimbursement Policies Incentivize Innovation

PPTA recognizes and appreciates that periodically evaluating payment and reimbursement methodologies ensures the sustainability of the healthcare system and safeguards patient access. When contemplating payment and reimbursement reforms, PPTA urges policymakers to consider the rapidly changing research and development (R&D) landscape and the critical role that payment and reimbursement policies play in incentivizing early-stage exploration and advancing therapies to patients.

The plasma protein therapeutics industry is a longstanding innovative engine within the biologics sector.[4] Currently, the industry has a robust pipeline comprising over 100 therapeutic targets, of which nearly 25% are in the preclinical stage.[5] However, the promise of these therapies is threatened by scientific and market forces currently challenging the greater biotechnology and life sciences sector. These challenges include:

- A significant rise in the investments and resources necessary to develop safe and effective therapies due to the targeting of increasingly complex rare disease targets;
- Shrinking patient populations arising from advances in elucidation of disease etiology, pathogenesis, pathophysiology, and heterogeneity;
- Growing scientific and regulatory complexities associated with the shift to more personalized therapeutic development; and
- The inherent risks associated with developing next-generation biologic treatments.

While these challenges are positive in the sense that that they reflect the rapid advancement of R&D technologies and the biomedical community's growing understanding of disease state pathophysiology (thereby enabling the discovery and development of more effective and targeted therapies), they have contributed to a

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[4] For a description of the discovery and development of the modern plasmapheresis process used to separate blood and plasma, giving rise to the availability of therapeutically useful plasma, and ultimately establishing the foundation for future innovations that led to plasma protein isolation and therapeutic development, see *Production of Plasma Proteins for Therapeutic Use*, Bertolini J., Goss N., Curling J, Wiley & Sons (2013).

[5] *See* Member company product portfolio and pipeline reports.

significant growth in R&D costs[6] and a rise in the number of research and development projects that fail before reaching patients.[7]

While the plasma protein therapeutics industry is working on ways to reduce the risks and costs associated with developing the next generation of biologic therapies, downward pressure from public payers is amplifying the impact of these challenges. Across the life sciences industry, this economic pressure is contributing to earlier therapeutic candidate terminations by innovators, and by extension, reducing the number of potential lifesaving therapies that will be available to patients in the future.[8] Accordingly, it is imperative that the increasingly complex, risky, and costly nature of therapeutic development be taken into consideration as payment and reimbursement methodologies are reformed. In particular, policymakers should avoid policies that indiscriminately reduce payment and reimbursement rates without consideration for the evolving R&D landscape, as this can result in a chilling effect on upstream innovation and impede future patient access to lifesaving therapies.

2. Ensure that Payment and Reimbursement Policies Maintain Patient Access

As the *21st Century Cures* initiative progresses, PPTA urges the Committee to keep patients at the center of the discussions. The plasma protein therapeutics industry makes this recommendation based on the experience of the industry and patients during the implementation of reimbursement changes enacted as part of the Medicare Modernization Act of 2003 (MMA), which demonstrated the unintended consequences of well-intentioned payment reforms.

Beginning in 2003, the MMA mandated that reimbursement for intravenous immune globulin (IVIG) under Medicare Part B change from average wholesale price (AWP) to average sales price (ASP). This resulted in a significant reduction in how physicians were reimbursed by Medicare for administering therapies. At these reimbursement levels, many physicians could no longer afford to purchase and administer IVIG, and therefore discontinued providing in-office infusion services. An unintended consequence of the MMA's change to reimbursement was that between 2003 and 2006, IVIG treatment in the physician office setting fell from 54% to 31%,[9] and by 2010, 64% of Medicare IVIG, immune compromised, patients were treated in hospital outpatient

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[6] DiMasi JA, Hansen RW, Grabowski HG. 2003. The price of innovation: new estimates of drug development costs. Journal of Health Economics 22(3): 141–185 (observing an approximate 50% increase in drug development costs from the 1990s to the 2000s).

[7] KMR Group, *R&D Performance—Pharmaceutical Benchmarking Forum* (2012) (observing that 3% of R&D projects that successfully progress from the preclinical stage to phase I clinical testing will succeed in the remaining stages of clinical development to be approved by the FDA).

[8] Bruce Booth & Rodney Zemmel, *Prospect for Productivity*, 3 Nature Review Drug Discovery 451, 456 (2004) (Highlighting that "as health care cost containment becomes an increasingly important issue for payers and governments, the pressure on the current R&D model will probably make [continued productivity] unsustainable for the industry"); *see also* Carmelo Giaccotto, et al., *Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry*, 48 J. L. Econ. 195, 212 (2005) (conducting a simulation study predicting that "the capitalized value of pharmaceutical R&D spending would have been about 30 percent lower if the federal government had limited drug price increases to the same rate of growth as the general CPI during the period 1980-2001").

[9] The Moran Company, *2003-2010 Trends in IVIG/SCIG utilization by PID patients, by site of service*, (December 21, 2012).

departments versus 33% in physicians' offices.[10] This example demonstrates that changes to reimbursement have the potential to immediately and dramatically affect patient access to care, resulting in long-term, irreversible adverse events.

Access issues can be especially devastating for patients living with chronic and rare diseases, such as patients treated with plasma protein therapies. For example, many IVIG patients are living with an immune deficiency or are immune-compromised. As a result, the most appropriate and safest – and presumably most cost-effective – site of care is often in the home, where these patients are not exposed to potential infections. Forcing IVIG patients to travel to hospital outpatient departments for infusions can not only be a significant hardship, but can lead to worse health outcomes (and resultant costs to Parts A and B from unnecessary hospital admissions and physician care).

Additionally, prior to being properly diagnosed and gaining access to treatment, many rare disease patients who rely on plasma protein therapies are often misdiagnosed for multiple years and sometimes decades.[11] Ensuring that these patients have insurance coverage that allows for uninterrupted access to the dispersed networks of specialists who best understand their rare conditions, and appropriate and timely access to the best possible therapies is critical to maintaining and improving patient health outcomes.

A 2008 study conducted by the Immune Deficiency Foundation (IDF) found that on average 14 percent of patients diagnosed and living with primary immune deficiency (PID) discontinue utilization of IVIG replacement therapy due to a lack of insurance coverage.[12] The findings of the 2008 study also demonstrate that such discontinuance increases the risk for those patients of permanent impairment of lung function, mobility, digestive function, and vision and hearing. Once PID patients begin or resume treatment the functional impairments arising from non-treatment suppress the effectiveness of IVIG. Accordingly, not only do discontinuances and gaps in insurance coverage undermine the health of already immune-compromised patients, but they also serve to increase the overall costs of treatment and care to the healthcare system. An estimated 4,000 PID patients who are under the age of sixty-five receive Social Security Disability Insurance payments due to the functional impairments arising from their disease.

Based on the industry's experiences with changes in reimbursement, PPTA urges policymakers considering payment and reimbursement reforms to incorporate strict safeguards for patient access to all sites of care, and to ensure that changes to reimbursement do not present a barrier to timely and appropriate patient access of the therapy prescribed by their physician. For example, in 2013, recognizing the potential for improved health outcomes and savings to Medicare, Congress passed the Medicare IVIG Access Act (P.L. 112-242), enacting a three-year demonstration project that allows for the payment of home infusion services for Medicare primary immune deficient (PID) patients. The passage of the IVIG Access Act will not only benefit patients living with

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[10] *Id.*

[11] *See, e.g.,* Vogelmeier C., et al., *Alpha-1-antitrypsin deficiency. Summary of a scientific symposium at the conference of the Swiss Pneumologic Society on April 16th, 2009*, 63 Pneumologie 12, 718-25 (2009) (Noting the clinical findings that the "time delay between the start of respiratory symptoms and the correct diagnosis of alpha-1-antitrypsin (AAT) deficiency is often 6 to 8 years").

[12] Marcia Boyle, Christopher Scalchunes, Impact of intervenous immunoglobulin (IVIG) treatment among patients with Primary Immunodeficiency diseases, Pharmaceuticals Policy and Law 10 (2008) 133–146.

chronic and rare diseases, but stands as a model for patient-centered policymaking that should be applied through the *21st Century Cures* initiative.

3. Consistently Engage Stakeholders to Ensure Payment and Reimbursement Methodologies Advance in Parallel to Technological Improvements

Recognizing the logarithmic trajectory of biomedical innovation, PPTA urges policymakers to expand opportunities for stakeholders to inform consistent advancement of payment methodologies through regular public meetings with CMS aimed at preparing the agency for next-generation technologies. For example, diagnostics and gene therapies are experiencing rapid innovation and will present distinct new challenges, including appropriate patient identification, therapeutic delivery and administration, effective treatment regimens, and unique pharmacoeconomics.[13] As policymakers evaluate payment methodologies, it is vital to appreciate these evolving advances and challenges.

Compounding the importance of consistently and predictably advancing payment and reimbursement methodologies are the complex and hard-to-treat disease states that many of these medical technologies are targeting. Lifelong, genetic diseases such as hemophilia and alpha-1-antitrypsin deficiency, which are currently effectively treated with coagulation factors and plasma-derived alpha-1 proteinase inhibitor, are seeing significant advances in promising next-generation therapies and diagnostics. As exciting as these advances are, without effective reimbursement rates and models, innovation will falter and patient access will suffer.

Accordingly, PPTA recommends Congress authorize and CMS implement a "public workshop" approach to stakeholder engagement on complex scientific issues, similar to that employed by FDA.[14] FDA's public engagement procedures, while still progressing and improving, offer a model worthy of replication by other agencies that must maintain a cutting edge understanding of scientific advancements to ensure innovation and patient access do not suffer. FDA regularly holds public workshops to bring together a broad range of stakeholders to discuss current and future standards development activities for next-generation medicines and medical technologies. These workshops serve to transparently communicate FDA's intended approach to regulating next-generation medical technologies, while also providing stakeholders opportunities to provide expert advice and inform the advancement of regulatory science. Similar engagement efforts by CMS would advance predictability and transparency in payment policymaking, while also providing CMS access to stakeholder expertise and perspectives. Importantly, improving public engagement by CMS in this way will allow the agency to maintain the relevancy and effectiveness of payment and reimbursement policies in parallel to advances in therapies and treatments.

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[13] Patricia Danzon, and Adrian Towse, *The Economics of Gene Therapy and of Pharmacogenetics*, 5 Value in Health 1 (2002).

[14] *See E.g.* FDA Public Workshop, *Synergizing Efforts in Standards Development for Cellular Therapies and Regenerative Medicine Products*, http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm364114.htm (Last visited May 31, 2014).

II. DISCOVERY

The success of the discovery stage of innovation – as measured by the advancement in the scientific community's understanding of the underlying genetics and pathophysiology of diseases and the identification of possible treatment targets – is primarily determined by stable funding for what are often long-term projects as well as the availability of disease and patient-related data. Accordingly, PPTA urges the committee to consider ways in which the state of basic research funding and data availability can be improved.

1. Increase and Stabilize Public Funding for Basic Scientific Research

Patients are currently realizing the dividends of past investments made by the government in basic scientific research. PPTA recognizes the important role that basic research plays in the innovation continuum, and supports increasing and stabilizing basic research funding for National Institutes of Health (NIH). The history of the plasma protein industry demonstrates the importance of this investment: the industry's genesis can in part be traced to government-funded research during World War II that aided the early-stage development of fractionation technologies, which act as the first step in isolating therapeutic proteins from human-donated plasma.[15] As such, PPTA is keenly aware that basic scientific research can play a pivotal role in laying the groundwork for future medical innovation, and potentially, spark the formation of entirely novel industries. Accordingly, PPTA encourages the committee to increase funding for basic research, particularly as it relates to rare diseases where research is more difficult and costly to conduct[16] and funding levels are traditionally lower relative to common disease states.[17]

2. Mitigate Barriers that Impede the Development of a Robust Body of Research Focused on Rare Diseases

As leading innovators targeting rare diseases, plasma protein therapeutics manufacturers have identified certain barriers to research related to rare diseases, which could in part be mitigated by collaboration between the public and private sectors. These challenges include:

- Difficulties developing fundamental incidence, prevalence, and outcomes-focused data among dispersed rare disease patient populations, which

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[15] Roger Lundlad, *Biotechnology of Plasma Proteins*, CRC Press (2013) (detailing the defense department's role in aiding the early-stage development ethanol fractionation).

[16] Institute of Medicine Report, *Rare Diseases and Orphan Products, Accelerating Research and Development* (2013).

[17] *See* NIH, Categorical Spending Table, *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)* (March 7, 2014), http://report.nih.gov/categorical_spending.aspx, last visited May 29, 2014.

challenge researchers seeking to identify the genetic and pathophysiological underpinnings of rare diseases; and

- A lack of centrally organized and publicly accessible databases providing rare disease-focused animal models and pathobiology and pathophysiology information generated by researchers from public, academic, and non-profit institutions, as well as industry, which impedes the translational capacity of rare disease researchers and clinicians.

Accordingly, PPTA encourages the committee to require prioritization of rare disease research efforts as part of the growing number of collaborations between FDA, NIH, the Centers for Disease Control and Prevention (CDC), the Patient Centered Outcomes Research Institute (PCORI), and other federal agencies that are focused on improving basic research. For example, the National Patient Centered Research Network (PCORnet), a promising partnership between PCORI, NIH, and multiple other academic institutions, features a task force on rare diseases that aids researchers across the country overcome research barriers that are unique to rare disease research.[18] The PCORnet model of collaboration and rare disease prioritization is a paradigm worthy of replication; yet, integration of a rare disease focus in PCORI's efforts required special advocacy by patients and stakeholders. Given the power of these collaborations to overcome the specific barriers facing rare disease researchers, PPTA recommends that as collaborations and cross-agency partnerships focused on improving basic research expand and grow in number, rare disease-focused functions be a required element of the collaboration.

III. CLINICAL DEVELOPMENT

1. Improve Regulatory Predictability Through Timely Rulemaking Procedures

In recent years, the FDA has successfully leveraged increased funding and new congressional authority to develop new review pathways and accelerate lifesaving therapies to patients. PPTA applauds these efforts, and supports the goal of advancing a collaborative regulatory environment that ensures that safe and effective therapies reach patients at the fastest possible rate. However, we believe that more can be done, particularly in the areas of consistency and predictability.

To help realize the promise of these new review pathways, PPTA urges Congress and the FDA to examine ways to increase the timeliness of agency rules. Too often, proposed rules linger for years before finalization. For example, a 2003 proposed rule, Safety Reporting Requirements for Human Drug and Biological Products, was published on March 14, 2003, and its comment period closed in October 2003; however, the rule was not finalized (and then, only in part) until 2010.[19]

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[18] *See* PCORnet, Rare Disease Task Force mission, http://www.pcornet.org/task-forces/rare-diseases/ (Last visited May 31, 2014).

[19] Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (21 CFR Parts 312 and 320) (2010).

Given the rapid pace of innovation in the biomedical sector, large gaps between rule proposal and finalization deprives the agency of the most recent data and accumulated industry experience on the subject at issue. This practice also makes it extremely difficult for industry to anticipate and adjust business practices ahead of new rules, and arguably deprives the public and stakeholders of a true opportunity for notice and comment.

More generally, these types of delays by the agency undermine regulatory predictability, an integral factor for ensuring the stability and efficiency of the innovation continuum. Accordingly, PPTA suggests that the Committee collaborate with the FDA to develop a process that delineates procedures for finalizing proposed rules. Such a process could reflect that, if a proposed rule is not finalized within a reasonable amount of time after the closing of the comment period, (*e.g.,* 24 or fewer months), then the proposed rule must be re-proposed for further comment.

IV. CONCLUSION

Thank you for your time and consideration of PPTA's comments on the *21st Century Cures* initiative. PPTA greatly appreciate the Committee's outreach to interested stakeholders, and we look forward to engaging in the initiative as it progresses.

Best regards,

[redacted]

Everett Crosland
Director, Federal Affairs
Plasma Protein Therapeutics Association
[redacted]

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Telecommunications Industry Association
21st Century Cures: A Call to Action
Comments on Questions Posed in the White Paper
June 1, 2014

I. Introduction

The Telecommunications Industry Association (TIA) hereby submits comments in response to the white paper "21st Century Cures: A Call to Action."

TIA is a trade association representing nearly 400 global manufacturers, vendors, and suppliers of information and communications technology (ICT), and engages in policy efforts specific to health ICT to promote a modern healthcare system that leverages innovative technologies to transform the way care is delivered and consumed. Many of TIA's member companies develop, manufacture, and supply health information technologies and medical devices, producing the tools that allow patients and health care providers to connect virtually anytime, anywhere. TIA would like to applaud the Energy & Commerce Committee for launching an initiative aimed at accelerating the discovery, development, and delivery of new treatments and cures to patients, and we thank the Committee for this opportunity to provide comments.

II. Encouraging Investment & Innovation

The United States' propensity for innovation has allowed us to maintain a global competitive edge and reap the economic benefits. As other countries seek to emulate our success and commit more resources to research and development, it is imperative that the United States maintain its leadership role as a hub for innovation. For this to continue, we must have effective policies in place that facilitate investment and innovation, and a regulatory framework that provides predictability and reduces barriers to innovation.

a. The United States Must Make Investment in Advanced Medical Device Technologies a National Priority

Decades of robust investment in the discovery, development, and delivery of new treatments and cures has made the U.S. a global leader in medical device innovation. Our successes have driven global competition and now other countries are increasing their own contributions to

research and development. In order to maintain our status as a global leader the U.S. must make investments in medical research a national priority. From 2007 to 2012, U.S. investment in biomedical R&D dropped from $131.3 billion to $119.3 billion, a -1.9% compound annual decline. During the same period, the Asia-Pacific region increased spending increased from $41.1 billion to $62 billion, including a 5.7% compound annual growth for Japan and a 32.8% compound annual growth rate for China (from $2 billion in 2007 to $8.4 billion in 2012)[1]. Much of the decline in U.S. investment came from the private sector, where its share of global R&D expenditure declined from 50.4% in 2007 to 42.3% in 2012.

This trend is very troubling indeed and potentially damaging, threatening our status as global leader. Certainty in sustained or increased federal investment in R&D is important and will help contribute to US leadership, but government policies must also provide incentives and facilitate strategic and robust investment from the private sector. A permanent R&D tax credit will not only create jobs but will create billions of dollars in additional R&D investment. Making it permanent will also promote certainty for businesses.

b. The Health Care System of the Future Should Realize the Potential of Remote Patient Monitoring

A modern, 21st century healthcare system must leverage innovations in communications technologies. Innovative technologies are needed that connect patients, health care providers, and medical professionals virtually anywhere, and facilitate ongoing care and treatment wherever and whenever it is needed. Outdated regulations that have restricted the use of telehealth have long been a hindrance to progress in this space. As a notable example, Section 1834(m) of the Social Security Act has resulted in arduous restrictions on telehealth services (*see* 42 CFR § 410.78). The ICT manufacturer, vendor, and supplier community urges for Congress to work towards realization of a connected healthcare system by removing barriers to the utilization of advanced technologies.

The known benefits of remote patient monitoring services include improved care, reduced hospitalizations, avoidance of complications and improved satisfaction, particularly for the chronically ill.[2] Remote patient monitoring of patient-generated health data (PGHD) must be

[1] *See* Chakma, et al, "Asia's Ascent—Global Trends in Biomedical R&D Expenditures." *New England Journal of Medicine* 370.1 (2014), DOI: 10.1056/NEJMp1311068

[2] *See, e.g.*, U.S. Agency for Healthcare Research and Quality ("AHRQ") Service Delivery Innovation Profile, *Care Coordinators Remotely Monitor Chronically Ill Veterans via Messaging Device, Leading to Lower Inpatient*

utilized for any health care system to realize its full potential. The National eHealth Collaborative ("NeHC") has defined PGHD as "Health-related data created, recorded, gathered, or inferred by or from patients or their designees to help address a health concern."[3]. Involving this data will engage patients in their own care, can lead to improved lifestyle choices and improve overall health.[4] There are also significant potential for cost savings, with a recent study predicting that remote monitoring will result in savings of $36 billion globally by 2018, with North America accounting for 75% of those savings.[5] Policies must be in place that enable greater use of these dynamic solutions and promote greater development and opportunities for health care delivery.

c. Setting Appropriate Goals in Advancing Healthcare: a Connected Continuum of Care

While national and global efforts to develop, integrate, and utilize innovative technologies that enable eHealth and telemedicine have allowed this industry to mature, we must continue looking for ways to maximize the potential of health ICT. Regulations and policies should reflect the dynamic and transformative nature of these technologies, and shouldn't stifle innovation. Current areas of focus, particularly on the agency level, remain on electronic health records (EHRs) and EHR interoperability. Meanwhile, there is a true need for federal priorities to address the full potential of the health information technology ecosystem which is comprised of many technologies, including medical remote monitoring products that are enabled with wired, wireless and mobile ICT. Based on the potential benefits that remote monitoring and PGHD can provide to countless Americans, we encourage Congress to approach efforts to advance healthcare past interoperability of EHRs, and to fully support a connected health ICT ecosystem. Embracing the diversity of solutions will allow for innovative improvements at each stage along the continuum of care. Consciously taking a broader focus as we describe above

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Utilization and Costs (last updated Feb. 6, 2013), *available at* http://www.innovations.ahrq.gov/content.aspx?id=3006.

[3] *See* NeHC, *Patient Generated Health Data White Paper* (Apr. 2012) at 2-3, available at http://www.nationalehealth.org/ckfinder/userfiles/files/PGHD%20White%20Paper_April%202012.pdf.

[4] *See, e.g.*, Sanjena Sathian, "The New 21st Century House Call," Boston Globe (July 29, 2013), *available at* http://www.bostonglobe.com/lifestyle/health-wellness/2013/07/28/century-house-call/tdupWvOQI6b3dKdKcEgdGM/story.html.

[5] *See* Juniper Research, *Mobile Health & Fitness: Monitoring, App-enabled Devices & Cost Savings 2013-2018* (rel. Jul. 17, 2013), available at http://www.juniperresearch.com/reports/mobile_health_fitness.

would be a noteworthy step towards encouraging innovation and investment into new technologies that will improve care, reduce hospital visits, and save lives.

III. Conclusion

Telehealth continues to change the way that health care is delivered and consumed. As we continue looking forward, it is imperative that we have policies and practices in place that enable the development of this important industry. We must continue to harness 21st century advances in science and technology, including innovative communications technologies, to ensure that Americans reap the benefits of a modern health care system.

Thank you again for your leadership, and we look forward to working with you on these important issues. For more information, please contact Danielle Coffey at (703)-907-7734 or by email at dcoffey@tiaonline.org.

Sincerely,

[redacted]

Grant Seiffert
President